Symptomatic and Stenotic Developmental Venous Anomaly with Pontine Capillary Telangiectasia: A Case Report with Genetic Considerations

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Abstract

Stenotic developmental venous anomalies (DVAs) often present with neurological deficits. In addition, cerebral capillary telangiectasia (CCT) coexisting with DVA is rarely encountered, and its pathophysiology, including the underlying genetics, and appropriate management remain uncertain. A 46-year-old man without any medical history of note was referred to our hospital with gradually worsening cerebellar ataxia. Two months after symptom onset, ataxic dysarthria and gait emerged. Brain magnetic resonance imaging showed CCT occupying the pons and left cerebellar peduncle. Subsequent catheter angiography demonstrated a DVA leading from the mass into the cavernous sinus with marked outlet stenosis and flow stagnation. We hypothesized that venous congestion was the source of gradual neurological deterioration and therefore initiated anticoagulation. Symptoms showed mild improvement, and his neurological status has remained stable as of 1 year after symptom onset. Whole-exome sequencing of germline DNA did not reveal any rare variants in genes previously reported as pertinent to vascular malformations. Anticoagulation may be a useful option in patients with non-thrombotic, stenotic DVA for whom neurological status did not improve under expectant management. Genetic analysis of this patient did not reveal any pathogenic mutations, and further investigation of somatic mutations is necessary to elucidate potential genetic causes.

Keywords: developmental venous anomaly, capillary telangiectasia, venous hypertension, genetics

Introduction

Stenosis is one of the leading causes of symptomatic developmental venous anomalies (DVAs), usually treated by conservative management.[1] However, no consensus has been reached on how to manage symptomatic DVAs with stenosis and without venous thrombosis if conservative treatment fails.

On the other hand, cerebral capillary telangiectasia (CCT) concomitant with other vascular malformations (i.e., DVA and cavernous malformation) is rarely encountered. If a combination of these vascular malformations causes neurological deficits, the CCT is usually not the culprit.[2]

We described herein the clinical course of a patient with symptomatic DVA and CCT who had a family history of vascular malformation and in whom neurological deficits did not improve with expectant management alone, necessitating additional treatment. In addition, considering the family history, we performed whole-exome sequencing of germline DNA for the patient and discussed the results herein.

Case Report

A 46-year-old man without any medical history of note was referred to our hospital with gradually worsening cerebellar ataxia. He had started to feel intention tremor 7 months prior to this referral. Two months after the onset of this symptom, ataxic dysarthria and gait emerged. He underwent magnetic resonance imaging (MRI) of the brain at a nearby clinic as a primary survey, revealing an abnormal mass in the brainstem. For further surveillance, he
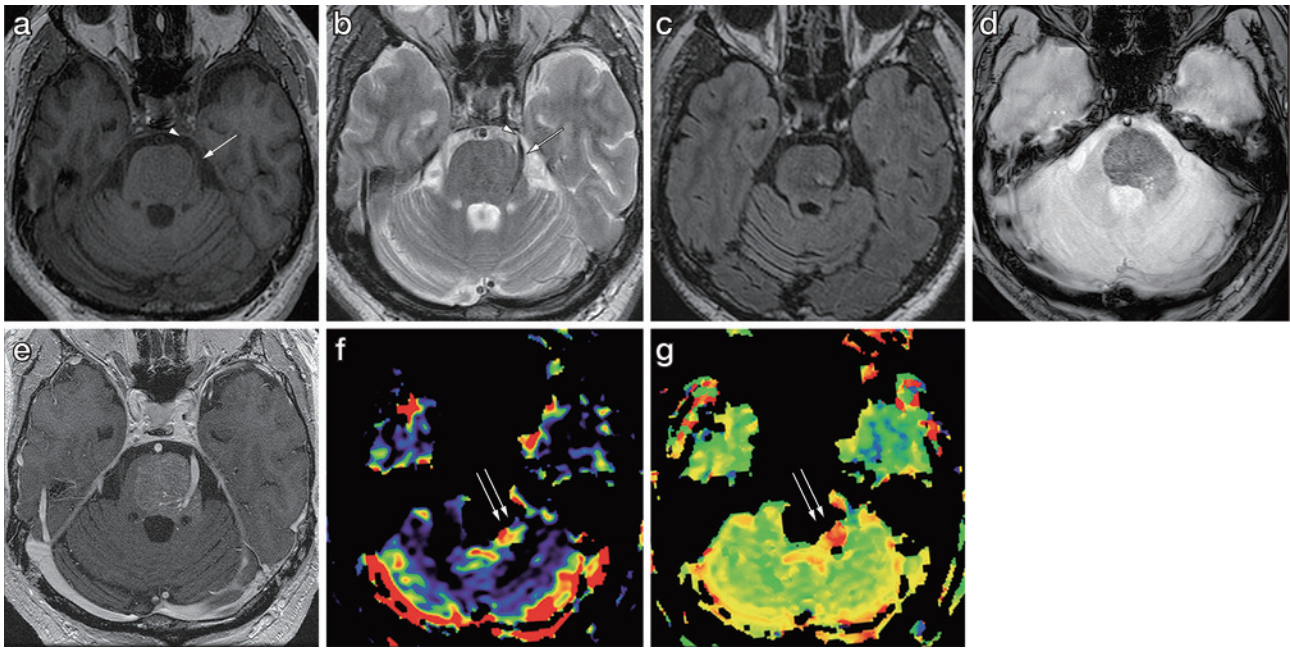
Fig. 1   Magnetic resonance imaging on admission.
a) T1-weighed imaging, axial view. The outlet of the developmental venous anomaly (DVA) (arrow), medially adjacent to the left trigeminal nerve, does not show intraluminal hyperintensity, implying that no thrombus is evident inside the stenotic draining vein (arrowhead).
b) T2-weighted imaging, axial view. A prominent draining vein from the left cerebellar peduncle indicates the DVA (arrow). Note the severe stenosis at the junction of the DVA and cavernous sinus (arrowhead).
c) Fluid-attenuated inversion recovery imaging. Faint hyperintensity is detected adjacent to the DVA.
d) T2* imaging shows moderately hypointense stippled lesions, compatible with a diagnosis of CCT.
e) Gadolinium-enhanced T1-weighted imaging shows faint stippled brush-like enhancement from the pons to the left cerebellar peduncle. This image also shows the DVA.
f) The cerebral blood volume computed with T2*-based perfusion-weighted imaging. Elevated cerebral blood volume is observed in the left superior cerebellar peduncle and the central lobule of the vermis (double arrows). The large signal defect in the pons corresponds to the T2* hypointense lesion.
g) The mean transit time computed with perfusion-weighted imaging. Prolonged mean transit time is also confirmed in the same region as seen in Fig. 1f (double arrows).

was admitted to our hospital.

Elicitation of family history revealed that his niece had multiple hemangiomas on her feet and postauricular area, albeit a more specific diagnosis (e.g., Klippel-Trenaunay syndrome) had not been established for her condition. The patient presented with significant ataxic dysarthria and gait disturbance without motor or sensory deficits on admission. MRI of the brain on admission showed a 4-cm hypointense mass occupying the pons and the left cerebellar peduncle (Fig. 1a-e). T2-weighted imaging demonstrated a prominent draining vein out of the mass into the cavernous sinus (Fig. 1b). T1-weighted imaging did not show any intraluminal hyperintensity in the draining vein, implying that venous thrombosis was unlikely coexistent (Fig. 1a). Fluid-attenuated inversion recovery imaging demonstrated minimal intraparenchymal hyperintensity adjacent to the DVA (Fig. 1c). Gadolinium-enhanced T1-weighted imaging also showed the draining vein with a faintly enhancing surrounding mass corresponding to the low-intensity area

on T2* imaging (Fig. 1d and e). Perfusion-weighted imaging exhibited elevated cerebral blood volume and prolonged mean transit time in the left superior cerebellar peduncle and the central lobule of the vermis, denoting venous congestion (Fig. 1f and g). These results suggested a diagnosis of CCT with concomitant DVA. In the light of the family history of vascular malformations, a thorough survey of vascular malformations in the trunk on contrast-enhanced computed tomography revealed no other vascular lesions.

Digital subtraction angiography did not show any arteriovenous shunts or lesional stains. Still, the outlet of the DVA was severely stenotic in the proximity of the cavernous sinus (Fig. 2a-d) and caused significant flow stagnation (Fig. 2e).

Continuous heparin infusion was initiated after diagnostic angiography, considering possible thrombus formation at the stenotic site and the slowly deteriorating neurological status. We administered heparin for 1 week, followed
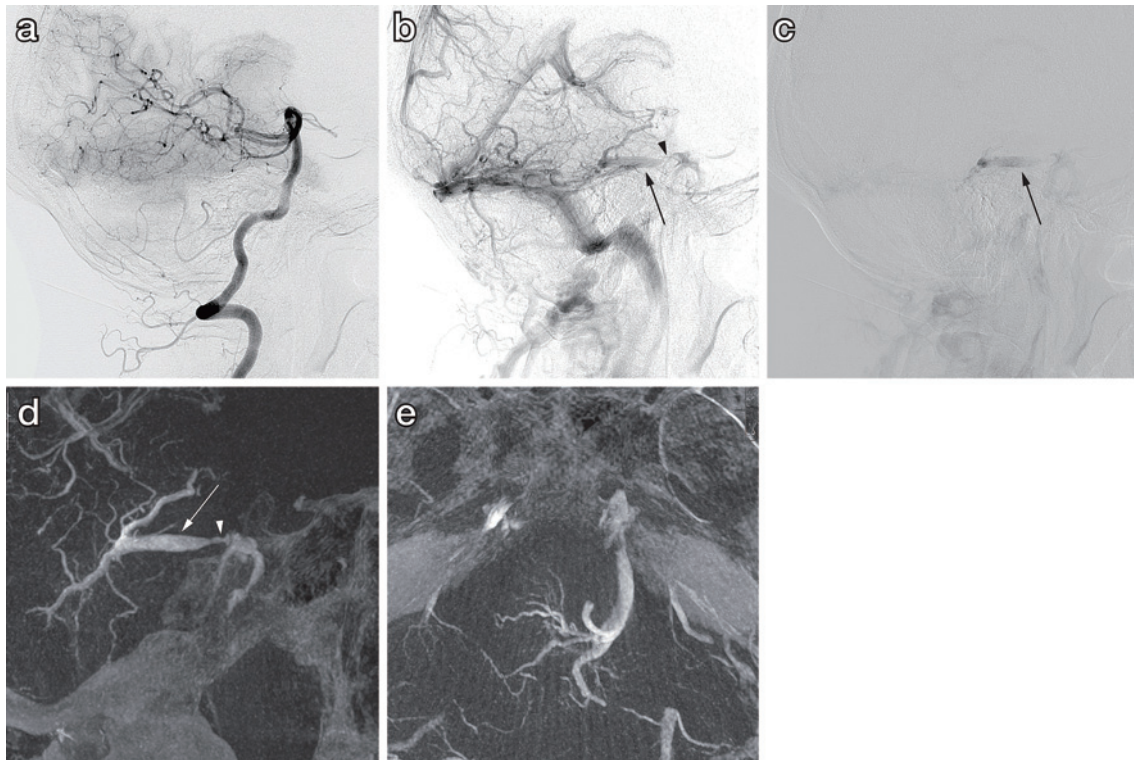
Fig. 2 Digital subtraction angiography and three-dimensional rotational angiography.
a) Left vertebral arteriography, lateral view. In the arterial-to-capillary phase, no capillary stain or arteriovenous shunt is observed in the brainstem parenchyma.
b) Left vertebral arteriography, lateral view, venous phase. The angiogram shows a prominent vein draining from the pons into the cavernous sinus (arrow). The outlet of the DVA is markedly stenotic (arrowhead).
c) Late-phase venogram, lateral view, showing persistent pooling of the contrast medium in the DVA, particularly in the intraparenchymal segment.
d) Sagittal multiplanar reconstruction of three-dimensional rotational venography of the DVA shows the stenotic site at the veno-dural junction. The arrow and arrowhead indicate the same structures as in Fig. 2b.
e) Axial multiplanar reconstruction of the three-dimensional rotational venography of the DVA shows a typical finding of DVA (caput medusae).

by treatment with a direct oral anticoagulant (edoxaban 60 mg/day). Cerebellar symptoms showed mild improvement, but slight gait disturbance remained. The patient was discharged on hospital day 15 and has since been followed up on an outpatient basis. Cerebellar symptoms were unchanged at 6 months after discharge, and administration of edoxaban was ended. Follow-up MRI at that time did not show any signal changes in the lesion. His neurological status was stable at 1 year after discharge.

In an attempt to clarify the genetic background of the DVA and concomitant CCT against the background of a family history of vascular malformations, we performed whole-exome sequencing of the germline DNA. Written informed consent was obtained from the patient for the genetic analysis.

Genomic DNA was obtained from peripheral blood leukocytes using a DNA extraction kit (Talent SRL, Trieste, Italy).

Whole-exome sequencing was performed with SureSelect

V7 kit (Agilent Technologies, Santa Clara, USA). Sequencing data were generated using the Illumina HiSeq 2500 sequencer and the 100-basepair paired-end sequencing protocol across rapid flow cell lanes. Sequencing reads were aligned to the reference human genome (hg19). Detailed conditions will be provided on reasonable request.

We checked for possibly pathogenic variants of 43 genes previously reported as pertinent to vascular malformations: *ACVRL1*, *AKT1*, *BRAF*, *CAMTA1*, *CCBE1*, *CCM2*, *ELMO2*, *ENG*, *EPHB4*, *FLT4*, *FOS*, *FOSB*, *FOXC2*, *GATA2*, *GDF2*, *GJC2*, *GLMN*, *GNA11*, *GNA14*, *GNAQ*, *HRAS*, *IDH1*, *IDH2*, *KIF11*, *KRAS*, *KRIT1*, *MAP2K1*, *MAP3K3*, *MYC*, *NRAS*, *PDCD10*, *PDGFRB*, *PIK3CA*, *PTEN*, *PTPN14*, *RASA1*, *SMAD4*, *SOX18*, *STAMBP*, *TFE3*, *TIE2*, *VEGFC*, and *VEGFR3*.[3-9] The analysis identified six variants (Table 1), but we did not identify any potentially pathogenic mutations in the patient.

Table 1 Information of outputted six variants in genes pertinent to vascular malformations

Genes	Chr	dbSNP150 rs-ID	Nucleotide change	Quality	Depth	CADD score	MAF		
							ALFA	1000 Genomes	ToMMo
CAMTA1	1	rs3810982	C>T	94	26	19.04	0.175	0.208	0.325
GATA2	3	rs78245253	G>C	78	23	22.9	0.000626	0.012	0.0404
		rs2335052	C>T	94	18	17.34	0.165	0.233	0.358
VEGFC	4	rs3062984	CTCATCAT >CTCAT	214	37	–	0.000358	–	–
PDGFRB	5	rs75748462	C>T	172	30	28	0.000158	0.00160	0.0425
FLT4	5	rs448012	G>C	98	16	22.9	0.393	0.417	0.497

ALFA, Allele Frequency Aggregator; Chr, chromosome; MAF, minor allele frequency; ToMMo, Tohoku Medical Mega-bank Organization

Discussion

We have reported a case with cerebellar ataxia and mixed DVA and CCT located in the left middle cerebellar peduncle and pons. Outflow restriction due to outlet stenosis of the DVA was presumed to represent the leading cause of neurological deficits. Neurological status worsened during conservative management but improved after a week of anticoagulation. Whole-exome sequencing was performed in this case, considering the family history of vascular malformations.

The initial MRI did not show significant perilesional edema but demonstrated a prominent T2* hypointense area implicating CCT or hemosiderin deposition. This radiographic feature is occasionally observed in patients with venous congestion,[10] especially those with dural arteriovenous fistula presenting dilated medullary veins (a pseudophlebitic sign).[11]

In a meta-analysis of CCTs, 6 of 52 cases showed concomitant DVA; symptomatic CCTs, as shown in our case, were observed in only 8 cases.[2] Symptoms in those 8 cases comprised headaches, seizures, facial pain, and hearing loss, all of which were milder than in the present case. According to other reports, hemorrhage associated with CCT almost always arises from an associated vascular malformation and rarely from the CCT itself.[12,13] McCormick et al. suggested that elevated venous pressure in a DVA leads to dilated microvasculature, representing acquired telangiectasia that evolves toward a cavernous malformation.[14] Given this hypothesis, we concluded that the symptoms were primarily caused by the outflow restriction of the DVA, not by the secondary CCT.

According to one literature review on symptomatic DVA, outflow restriction is presumed to represent one of the leading causes of symptoms[1] and has two major causes: thrombosis and stenosis. In the literature review, cases with outlet venous stenosis without clues for concomitant thrombosis were conservatively managed, whereas patients with venous thrombosis were basically treated with heparinization.[2] Anticoagulation has been suggested as the first-line treatment for symptomatic DVA with thrombosis, even in the presence of hemorrhage, similar to the treatment of cerebral venous sinus thrombosis.[15] However, in previous reports, stenotic DVA without thrombosis has rarely been treated with anticoagulation. In our case, the patient's neurological status had been gradually deteriorating during conservative management. Furthermore, the late venous phase of the angiography showed prominent flow stagnation. We administered anticoagulants, supposing that radiographically occult thrombus formation due to the stagnant flow caused his symptoms. Of note, the patient's condition subsequently improved. Although this patient might have spontaneously recovered, anticoagulation represents an option in patients with DVA and non-thrombotic outlet stenosis for whom neurological status does not improve under expectant management. Angioplasty can be a treatment option to improve outflow restriction, but balloon angioplasty of intracranial veins carries a high risk of hemorrhage, and stent deployment is also associated with thrombosis. To date, no reports have described endovascular treatment for DVA.

The most important limitation of this report is that no unequivocal signs supported the hypothesis that venous congestion caused the patient's acute neurological deterioration. We did not perform perfusion-weighted imaging or catheter angiography after recovery of his neurological status. Moreover, the patient's neurological status did not deteriorate even after stopping oral anticoagulation therapy. If anticoagulation indeed relieves the symptoms of DVAs associated with outflow restriction and subsequent venous congestion, further investigations are required to collect more reliable evidence.

The pathophysiology of DVA with CCT possibly involves a pathogenic genetic disruption, but our analysis failed to

identify any causative mutations. Our patient had a family history of vascular malformations, implying that the DVA and CCT may involve underlying germline mutations. Unfortunately, pathogenic variants were not found among the 43 selected genes, but the genetic analysis in this report had some limitations. First, we did not obtain a blood sample from the patient's niece, who had hemangiomas in the postauricular area and feet. Specifically, the whole-exome sequencing performed for this patient could have revealed mutations in common with the niece. Second, we only analyzed variants previously reported as pertinent to vascular malformations. As described above, other hidden mutations might have been present. Third, only germline mutations, which all cells in the patient had in common, were screened for in the blood sample. Theoretically, the combination of CCT and DVA in this patient may involve underlying somatic mutations (i.e., lesional tissues may have had specific mutations that other tissues in this patient did not have) associated with vascular malformations, such as *PIK3CA*.[16] Unlike tumors or arteriovenous malformations, the tissue of DVA cannot be surgically obtained since DVAs function as a collector of normal drainage. As with DVA, CCT is generally unresectable due to the intervening cerebral parenchyma, unlike cavernous malformations.[2,17] In other words, if histological specimens had been obtainable, somatic mutations could have been discovered.

Conclusions

We have reported a case of symptomatic and stenotic DVA with CCT that required anticoagulation. Venous hypertension due to severe outflow restriction in the DVA possibly led to dilation of microvasculature, representing acquired CCT. In addition, anticoagulation may be an option in patients with DVA showing non-thrombotic outlet stenosis for whom neurological status does not improve under expectant management. Whole-exome sequencing of germline DNA for the patient did not reveal any rare variants of the genes reported as pertinent to vascular malformations. Further investigation of somatic mutations is necessary to unveil hidden genetic causes.

Ethics Approval

This study was approved by the Human Genome, Gene Analysis Research Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval number 3516; approval date, September 12, 2011).

Abbreviations

CCT, cerebral capillary telangiectasia; DVA, developmental venous anomaly; MRI, magnetic resonance imaging

Conflicts of Interest Disclosure

The authors declare no conflicts of interest (COI) concerning the materials or methods used in this study or the findings specified in this paper. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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