*Original Article*

Variations and management for patients with craniocervical junction arteriovenous fistulas: Comparison of dural, radicular, and epidural arteriovenous fistulas

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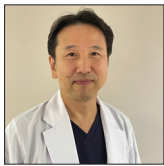
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ABSTRACT

Background: Craniocervical junction arteriovenous fistulas (CCJAVFs) are known to be rare, but variations and clinical behaviors remain controversial.

Methods: A total of 11 CCJAVF patients (M: F=9:2, age 54–77 years) were investigated. Based on the radiological and intraoperative findings, they were categorized into three types: dural AVF (DAVF), radicular AVF (RAVF), and epidural AVF (EDAVF).

Results: There were four symptomatic patients (subarachnoid hemorrhage in two, myelopathy in one, and tinnitus in one) and seven asymptomatic patients in whom coincidental CCJAVFs were discovered on imaging studies for other vascular diseases (arteriovenous malformation in one, intracranial DAVF in two, ruptured cerebral aneurysm in two, and carotid artery stenosis in two). Of these 11 patients, 2 (18.2%) had multiple CCJAVFs. Of 14 lesions, the diagnoses were DAVF in 5, RAVF in 3, and EDAVF in 6 (C1–C2 level ratio =5:0, 2:1, 3:3). Patients with DAVF/RAVF in four lesions with intradural venous reflux underwent surgery, although an RAVF remained in one lesion after embolization/radiation. Since all six EDAVFs, two DAVFs, and one RAVF had neither feeder aneurysms nor significant symptoms, no treatment was provided; of these nine lesions, one DAVF and one RAVF remained unchanged, whereas six EDAVFs showed spontaneous obliteration within a year. Unfortunately, however, one DAVF bled before elective surgery.

Conclusion: CCJAVFs have many variations of shunting site, angioarchitecture, and multiplicity, and they were frequently associated with coincidental vascular lesions. For symptomatic DAVF/RAVF lesions with intradural drainage, surgery is preferred, whereas asymptomatic EDAVFs without dangerous drainage may obliterate during their natural course.

Keywords: Craniocervical junction arteriovenous fistula, Dural, Epidural, Multiplicity, Radicular

INTRODUCTION

A craniocervical junction arteriovenous fistula (CCJAVF) is a rare and peculiar disorder causing subarachnoid hemorrhage (SAH), myelopathy, brain stem dysfunction, occipital neuralgia, or neck pain, although thoracolumbar spinal arteriovenous fistulas (AVFs) mainly affect men and usually cause slowly progressive myelopathy due to venous congestion.[11,33,34,41,45] A Japanese nationwide surveillance study documented that CCJAVFs accounted for 2.4% of all dural AVF (DAVF) patients.[12] Recent developments in neuroradiological modalities have provided high-quality, three-dimensional angioarchitecture images to accurately clarify the location of the shunt point. In the DAVF category, surgical treatment is preferred over endovascular treatment.[9,31,40,46] Shunt obliteration assisted by intraoperative indocyanine green (ICG) video angiography is becoming commonly used to understand the complex small vessel structure.[7] At present, spinal AVFs are generally categorized into DAVF, intradural AVF, and epidural AVF (EDAVF). However, several reports regarding radicular AVFs (RAVFs), which are present between the spinal cord and the dura mater, have recently been published.[4,18,21,35] Since RAVFs in the craniocervical junction, in particular, may have distinct characteristics, differential diagnosis is of great importance. To clarify their true nature, various radiological examinations and the medical charts of these complicated CCJAVFs were retrospectively analyzed, focusing on the shunting site, angiographical features, comorbidities, treatments, and outcomes.

MATERIALS AND METHODS

A total of 11 CCJAVF patients (nine males and two females; age range 54–77 years; mean age 67.5 years) managed at our institution between July 2007 and March 2021 were studied. This cohort included four symptomatic patients and seven asymptomatic patients. Two patients had SAH, one had myelopathy, one had tinnitus, and seven had no symptoms because they were incidentally found during examinations for other disorders, including ruptured cerebellar arteriovenous malformation (AVM) in one, ruptured tentorial DAVF in one, symptomatic optic canal DAVF in one, ruptured cerebral aneurysms in two, and origin of internal carotid artery stenosis in two. All lesions were recognized at the C1 or C2 level. All patients underwent a variety of examinations including magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and digital subtraction angiography (DSA) to identify feeding arteries, the precise location of the shunt point, draining veins, and the presence of a feeder aneurysm or varix. After recognizing CCJAVFs, coronal sections of MRI sequences such as 3D fast advanced spin echo (3D FASE, Vantage Titan 3T, Canon Medical Systems, Tochigi, Japan), 3D fast spin echo (CUBE, 3T Signa Excite HDx, GE Medical,

Chicago, USA), short Tl inversion recovery (STIR, Signa Excite Xl 1.5T, GE Medical), and fast imaging employing steady state acquisition (FIESTA, Signa Excite XL 1.5T, GE Medical) were additionally performed in five patients to clarify the fistula point in various surrounding anatomical structures.

Based on the currently proposed classification,[4] they were subdivided into five types: DAVF (Type 1), RAVF (Type 2), EDAVF with pial feeders (Type 3), EDAVF (Type 4), and perimedullary AVF (Type 5). As the definition of CCJAVF in this study, if the fistulous point was fed by dural arteries alone and was attached to the inner dura mater on MRI or angiography, this lesion was considered a DAVF. If the fistulous point was fed by dural and pial arteries and was located between the dura mater and spinal cord on MRI, CTA, DSA, or intraoperative findings, this lesion was considered an RAVF. If the epidural plexus or suboccipital cavernous sinus was opacified directly by any arteries in the arterial phase of DSA, it was considered an EDAVF.

As for treatment, microsurgery, transarterial embolization, or CyberKnife radiation therapy were considered depending on the symptoms and the patient's general condition. Follow-up DSA was conducted to confirm the fistulous lesion in most patients.

RESULTS

Of the 11 patients, 2 (18.2%) had multiple CCJAVFs: one patient with 3 synchronous EDAVF lesions at the C1 and C2 levels, and one patient with 2 metachronous bilateral EDAVF lesions at the C2 level.

Of a total of 14 lesions, 5 (35.7%) were diagnosed as DAVFs, 3 (21.4%) were diagnosed as RAVFs, and the remaining 6 (42.9%) were diagnosed as EDAVFs [Table 1]; the ratios of lesions at the C1–C2 levels were 5:0, 2:1, and 3:3, respectively. Neither Type 3 (EDAVF with pial feeders) nor Type 5 (perimedullary AVF) was present in any of the patients. Coincidental vascular lesions on the initial DSA were noted in 5 patients (45.5%), including a ruptured cerebellar AVM in 1 patient (case 1), symptomatic intracranial DAVF in 2 patients (cases 3 and 4), and ruptured intracranial aneurysm in 2 patients (cases 10 and 11); four of these patients presented with SAH. In addition to these cerebrovascular diseases, an osseous AVF in the middle cranial base occurred after CCJAVF onset in one patient (case 11).

With respect to angioarchitecture, in five DAVF lesions, preoperative angiography showed feeding arteries of the C1–C3 radiculomeningeal artery (RMA) in five and the external carotid artery (ECA) in one, whereas in three RAVF lesions, the C1–C3 RMA was involved in three lesions, the ECA in one lesion, and the anterior spinal artery (ASA) in two lesions. A tiny feeder aneurysm was found in one RAVF lesion, whereas a varix of the draining vein was found in one

Table 1: Summary of the CCJAVF patients.

S. No.	Age/sex	R/L	Initial symptom	Level	Feeder	Drainer	Aneurysm	Shunt point	Classification	Treatment	Result	Outcome	Comorbidities
1.	60/M	R	None	C1	RMA (C1, C2, C3)	Descend	-	Dural	Type 1	Surgery	Cure	GR	Cerebellar AVM, SAH
2.	63/M	R	None	C1	RMA (C1, C2)	Ascend>descend	-	Dural	Type 1	-	Remain	GR	ICAS
3.	67/M	L	None	C1	RMA (C1, C2, C3), APA	Ascend>descend	Varix	Dural	Type 1	-	Bleed	D	Optic canal dAVF
4.	68/M	R	None	C1	RMA (C1, C2, C3)	Ascend	-	Dural	Type 1	Surgery	Cure	GR	SPS dAVF, SAH
5.	77/M	R	Myelopathy	C1	RMA (C1, C2, C3)	Descend	-	Dural	Type 1	Surgery	Cure	GR	
6.	65/M	L	SAH	C1	RMA (C1, C2, C3)	Ascend>descend	Feeder aneurysm	Radicular	Type 2	Surgery	Cure	GR	
7.	75/M	L	SAH	C1	RMA (C1, C2, C3), ASA, APA, OA	Ascend	-	Radicular	Type 2	Embolization and CyberKnife	Remain	GR	
8.	73/M	L	None	C2	RMA (C2), ASA	RMV	-	Radicular	Type 2	-	Remain	GR	ICAS, CI
9.	73/M	R	Tinnitus	C1	PoMA (C1), OA	SCS	-	Epidural	Type 4	-	Cure	GR	
10.	54/F	L	None	C1	PoMA (C1)	SCS	-	Epidural	Type 4	-	Cure	SD	BA tip AN, SAH
		R	None	C1	PoMA (C1)	SCS	-	Epidural	Type 4	-	Cure		
		L	None	C2	RMA (C2)	EVP	-	Epidural	Type 4	-	Cure		
11.	67/F	L	None	C2	Prelaminar A (C2)	EVP	-	Epidural	Type 4	-	Cure	GR	ICPC AN, SAH, osseous AVF, VA-PICA AN
		R	None	C2	Prelaminar A (C2)	EVP	-	Epidural	Type 4	-	Cure		

CCJAVF: Craniocervical junction arteriovenous fistula, M: Male, SAH; Subarachnoid hemorrhage, RMA: Radiculomeningeal artery, ASA: Anterior spinal artery, APA: Ascending pharyngeal artery, OA: Occipital artery, GR: Good recovery, SD: Severely disabled, D: Dead, AVM: Arteriovenous malformation, ICAS: Internal carotid artery stenosis, dAVF: Dural arteriovenous fistula, SPS: superior petrosal sinus, SCS: Suboccipital cavernous sinus, RMV: Radiculomeningeal vein, EVP: Epidural venous plexus, ICH: Intracerebral hematoma, CI: Cerebral infarction

DAVF lesion. Of the six EDAVF lesions, they were supplied by the RMA in one, the ECA in one, the posterior meningeal artery in three, and the prelaminar artery in two. In all DAVF patients, the shunt point was identified in the caudal side of the dural penetration of the vertebral artery (VA) on an MRI coronal image or as an intraoperative finding. On the other hand, in RAVF patients, the shunt point was identified on the C1 nerve root on an MRI image in two patients and as an intraoperative finding in one patient. The draining vein was single in all patients in both groups. In DAVF patients, the draining vein ascended to the cranial side alone in one patient, descended to the spinal side in two, and was bidirectional through the radicular vein in two, whereas in RAVF patients, the draining vein ascended in one and was bidirectional in two. In EDAVF patients, three C1 lesions showed drainage to the suboccipital cavernous sinus, whereas three C2 lesions showed drainage to the epidural venous plexus.

Regarding management and outcomes, in the DAVF group, three patients underwent craniotomy, and drainer clipping was successfully conducted, whereas in the RAVF group, one patient underwent surgery, and one patient underwent coil embolization followed by CyberKnife therapy. No patient in either group had perioperative complications. In three DAVF patients who underwent microsurgery, the drainer was found to arise under the dural penetration of the VA

and the C1 spinal nerve root. In one RAVF patient who underwent microsurgery, the drainer originated directly from the C1 nerve root that was between the dura and spinal cord. All three DAVF patients and one RAVF patient had postoperative angiography to confirm complete obliteration. However, one patient with RAVF had a remaining lesion 2 years after CyberKnife treatment. In the DAVF group, four patients experienced good recovery, but one patient had fatal bleeding 2 months before the elective surgery. In the RAVF group, two operative patients recovered fully, and one patient was unchanged. In three EDAVF patients with six lesions, no aggressive therapy was conducted due to insignificant symptoms. Nevertheless, follow-up angiography or MR angiography 1 year later confirmed complete obliteration. As for the outcomes, two patients had good recovery, but one patient became severely disabled due to primary damage from the aneurysmal SAH.

CASE PRESENTATION

Case 1 (Patient no. 5)

A 77-year-old man had suffered from motor weakness of the left upper limb and bilateral lower limbs for a year and visited our institution. Sagittal MRI (T2WI) showed a hyperintense signal in the upper cervical spinal cord
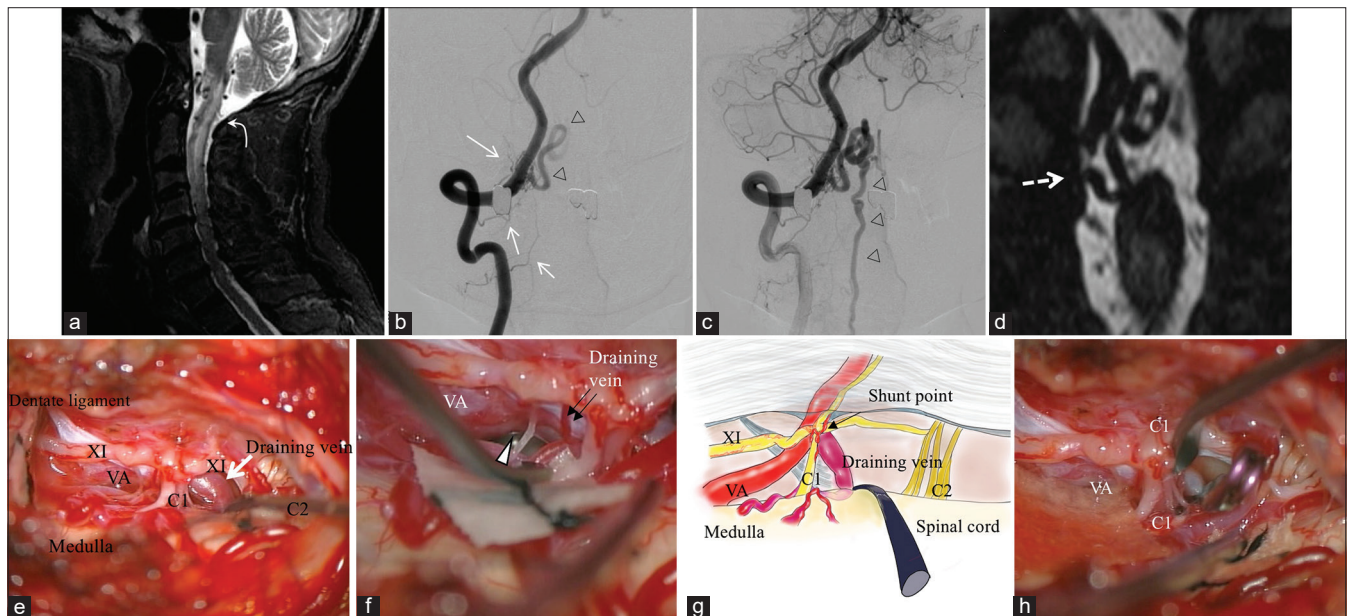

Figure 1: (Patient no. 5) (a) The sagittal section of T2WI shows a hyperintense area in the upper cervical cord and an abnormal flow void in the ventral side of the medulla oblongata. (b and c) Frontal view of the right VAG demonstrates an AV shunt at the foramen magnum level involving the RMAs of right C1–C3, with drainage by the radicular vein leading to the anterior medullary vein and anterior spinal vein (white arrowheads). (d) 3D FASE of MRI shows that the draining vein originates from below the VA dural penetration on the coronal view (dotted arrows). (e) In the prone position, the microscopic view demonstrates vessel structures that are relevant to this AV shunt, neurons, and a ligament. (f) Magnifying view confirms the shunt point where draining vein (double black arrows) seems to connect directly to the VA (white arrow head). (g) Schematic diagram of the operative view. (h) The main drainer is disconnected by clipping. RMA: Radiculomeningeal artery, VA: Vertebral artery.

[Figure 1a]. The right vertebral angiography showed a CCJAVF originating from the RMAs of C1, C2, and C3 with drainage to the anterior spinal vein [Figure 1b and c]. His three-dimensional rotational angiogram showed a single intradural draining vein just below the emergence of the VA from the dura. His MRI (3D FASE) demonstrated that the draining vein was present from the dural penetration region of the VA [Figure 1d]. He underwent surgical drainer ligation. The fistulous point was observed just behind the C1 nerve root and arising from VA dural penetration on the microscopic view [Figure 1e] and ICG video angiography [Figure 1f]. The intraoperative schema shows the angioarchitecture and microanatomy [Figure 1g]. Drainer clipping was subsequently performed [Figure 1h], and complete obliteration was confirmed by Doppler, ICG, and postoperative angiography. Thus, he was diagnosed with a DAVF. His symptoms improved after the operation, and he resumed his previous life.

Case 2 (Patient no. 6)

A 65-year-old man presented with SAH. Preoperative left VA injection demonstrated a CCJAVF on the left side that arose from the RMA of C1–3 with drainage to the radicular

vein connecting to the ascending intracranial vein and descending spinal vein [Figure 2a and b]. A tiny aneurysm was recognized on the feeder of the C1 RMA. It was noted that the oblique view showed a gap between the VA and the origin of the draining vein [Figure 2c]. Coronal MIP images of the CTA indicated that the fistulous point was located a short distance from the medial wall of the VA [Figure 2d]. He underwent craniotomy and C1 laminectomy in a prone position. After cutting the C1 dorsal root and dentate ligament, the fistula supplied by the dural and pial branches was found on the ventral root of the C1 nerve, although minimal pial supply was not identified on preoperative angiography [Figure 2e and f]. The intraoperative scene is depicted as a schematic diagram [Figure 2g]. The drainer was disconnected after a 10 min temporary test occlusion [Figure 2h], and the shunt completely disappeared. This patient was finally diagnosed with an RAVF based on the intraoperative findings.

Case 3 (Patient no. 11)

A 67-year-old woman was brought to our institution with an SAH due to an internal carotid-posterior communicating (IC-PC) artery aneurysm on the left side. Emergent partial
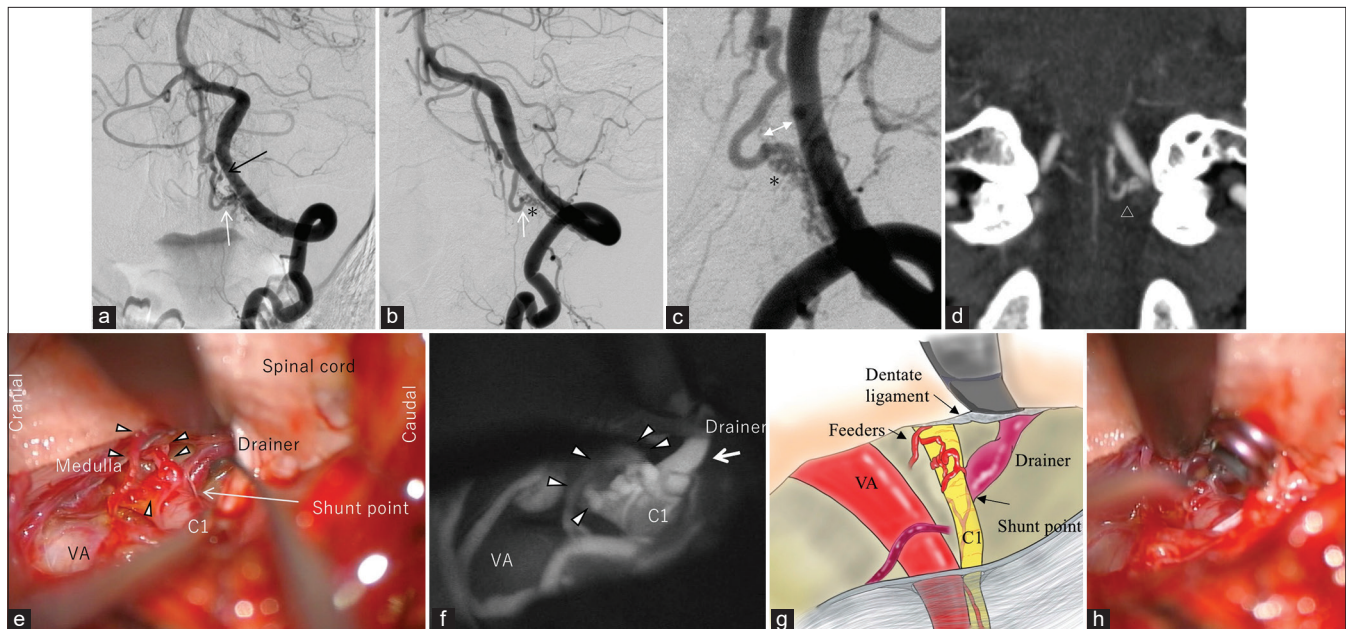

Figure 2: (Patient no. 6). Left vertebral angiogram ([a] frontal view, [b] LAO51, [c] LAO45 cranial 27) indicates the abnormal AV fistulous point (white arrow) arising from the RMAs of C1-3 with single drainage to the ascending and descending veins. A tiny aneurysm on the feeding artery (C1-RMA) is recognized (black arrow). The oblique view showing that the gap between the VA and ostium of the drainer ([c] bidirectional arrow) is noted. The shunt point seems to be tangled with fine vessels ([b and c] asterisk). (d) Coronal MIP images of CTA also confirm the shunt point (white arrowhead). (e) Intraoperative view after cutting the dorsal root of the left C1 nerve and dentate ligament. The ventral root of C1 is involved with tangled small vessels from the VA side and medullary side (white arrowheads). The main drainer originates from the C1 ventral nerve roots (white long arrow), and the angioarchitecture is depicted with ICG (f). (g) The schematic diagram of the intraoperative view. Permanent occlusion is performed (h). VA: Vertebral artery, RMA: Radiculomeningeal artery, CTA: Computed tomography angiography, ICG: Indocyanine green.

coil embolization was successfully conducted on the same day. Follow-up left VA injection on day 10 incidentally showed an AV fistula outside the dural sac (asterisk) supplied by the left C2 prelaminar artery, with drainage to the epidural venous plexus [Figure 3a-d]. Since this AVF was diagnosed as asymptomatic and was a low-flow EDAVF without intradural drainage, watchful observation was thought to be preferred to aggressive treatment. Follow-up angiography 2 months later confirmed the complete disappearance of this AVF [Figure 3e]. However, contralateral vertebral injection demonstrated a *de novo* EDAVF at the same level supplied by the prelaminar artery with drainage to the venous plexus [Figure 3f and g]. Furthermore, the left carotid artery angiography demonstrated a coincidental osseous AVF in the middle cranial fossa fed by an accessory meningeal artery with drainage to the maxillary vein [Figure 3h]. Both of the lesions were not treated because they were asymptomatic lesions without dangerous drainage. Additional clipping for the previously ruptured IC-PC aneurysm was performed after several days. Her follow-up angiograms detected the spontaneous disappearance of the osseous AVF after

2 months [Figure 3i] and of the right CCJ-EDAVF after 4 months as well [Figure 3j].

Case 4 (Patient no. 8)

A 73-year-old man with a history of old cerebral infarction, peripheral artery disease, diabetes mellitus, hypertension, and smoking had dizziness and visited our institution. His MRI demonstrated recurrence of cerebral infarction and severe internal carotid artery stenosis. On angiography, the left VA injection showed a CCJAVF consisting of nidus-like formation in the spinal canal at the C2 level arising from the left RMA and ASA with drainage to the radiculomeningeal vein of C1 and C2 leading to the epidural venous plexus [Figure 4a-c]. His CT angiography disclosed the fistulous point on the anterior root of the C2 nerve [Figure 4d and e]. His Gd-DTPA MRA also showed the abnormally enhancing lesion located mainly on the anterior cervical nerve root [Figure 4f and g]. Thus, this lesion was diagnosed as an asymptomatic RAVF. Elective treatment should be scheduled after the management for his cerebral infarction.

Figure 3: (Patient no. 11). Left VA injection on day 10 indicates the AV fistula outside the dural sac (asterisk) supplied by the left prelaminar artery of C2 (long black arrows) with drainage to the epidural venous plexus ([a and b] frontal view, [c and d] lateral view). (e) Two months later, follow-up angiography shows the disappearance of the lesion. (f and g) The contralateral vertebral angiogram, however, demonstrates the *de novo* fistula (asterisk) at the C2 level supplied by the prelaminar artery (black arrow) with drainage to the venous plexus. (h) At this examination, the carotid artery angiogram also shows another AVF (possibly an osseous AVF) in the middle cranial base fed by the accessory meningeal artery (single white arrow) with drainage to the maxillary vein (double white arrows). (i) Two months after its occurrence, it has disappeared. (j) The angiogram obtained 6 months following formation also confirms complete obliteration of the CCJAVF on the right side. VA: Vertebral artery, AVF: Arteriovenous fistula, CCJAVF: Craniocervical junction arteriovenous fistula.
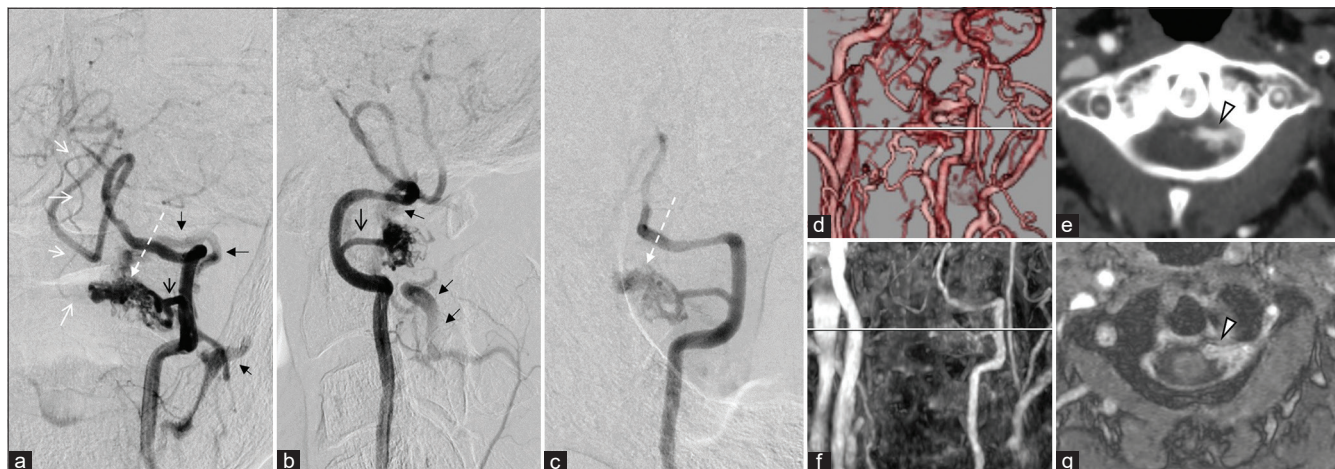
Figure 4: (Patient no. 8). (a-c) (a: frontal view, b: lateral view, c: right oblique view): left vertebral artery injection shows the CCJAVF consisting of nidus-like formation in the spinal canal at the C2 level (white dotted arrow), arising from the RMA (black open arrow) and the ASA with drainage to the radiculomeningeal vein of C1 and C2 to the epidural venous plexus (black closed arrow). (d and e) CTA discloses the fistulous point on the anterior root of the C2 nerve (white arrow head). (f and g) Gd-DTPA MRA also shows that the abnormally enhancing lesion is mainly located on the anterior cervical nerve root inside the dura mater (white arrow head). RMA: Radiculomeningeal artery, ASA: Anterior spinal artery, CTA: Computed tomography angiography, MRA: Magnetic resonance angiography.

DISCUSSION

Classification

Because spinal AVMs have many variations, they can be difficult to categorize clearly. The classification by Anson and Spetzler, which is based on the anatomy and appearance, has been generally used and includes type I: DAVF, type II: glomus AVM, type III: juvenile AVM, and type IV: intradural perimedullary AVF.[1] Another classification, which is based only on anatomical shunt location, simply divides spinal AVM into paraspinal, extradural, dural, and intradural.[20,26] Furthermore, the concept of epidural AVF was introduced by Spetzler,[32] and different clinical characteristics between lesions with retrograde intradural venous drainage and lesions without venous drainage were reported.[36] In addition, spinal epidural AVFs frequently involve the lumbar spine and form a venous pouch in the ventral epidural space draining into the perimedullary vein.[10]

Although a CCJAVF may be regarded as being in the category of spinal AVF, it includes the element of intracranial DAVF due to the high incidence of intracranial bleeding. However, recent developments in various neuroradiological modalities and accumulation of surgical experience have led to identification of a variation of AVF that includes the combination type of perimedullary and DAVF,[28,29] or RAVF on the spinal nerves located between the spinal cord and dura.[18,35] In the present study, the AVFs were categorized into five subgroups according to the classification proposed by a Japanese study group.[4] They were, however, exclusively designated as Type 1 (DAVF), Type 2 (RAVF), or Type 4

(EDAVF), because neither Type 3 patients nor Type 5 patients were seen in the current study.

Differential diagnosis, clinical course, and management

In the present study, the diagnosis was DAVF in five patients, RAVF in three patients, and EDAVF in three patients. Clinical behavior and management should be determined depending on the correct differential diagnosis. An RAVF is thought to form a shunt on a nerve root supplied by both the RMA and a pial artery. A Japanese, multicenter, research study described a total of 59 CCJAVF patients, including 37% with DAVF, 29% with RAVF, 24% with EDAVF, and 10% with perimedullary AVF; the study suggested an unexpectedly high prevalence of RAVF among all types. Moreover, the bleeding risk from RAVFs was 1.73-fold that from DAVFs.[4] The likely reasons are because they sometimes occur in association with a varix or feeder aneurysm, and they occur in the loose subarachnoid space on the nerve roots. In contrast, a DAVF has a relatively low risk of bleeding because this lesion emerges from the dura and is not present in the subarachnoid space. Distinguishing between these two types is essential in cases of asymptomatic lesions for determining the need for surgery. The shunt point cannot be detected easily during surgery because of the presence of complex, small vessels in a tight space. If these two types are distinguished at the time of diagnosis, time will be saved during the operation, since we can identify the shunt point quickly and correctly.

Regarding the two differential preoperative diagnoses, an RAVF is usually supplied by the ASA or lateral spinal artery, but involvement of these arteries is thought to be rare in

DAVFs. Because these lesions, however, are very small and have complicated angioarchitecture, judgment is not always easy. In fact, one of our three RAVF lesions failed to show a faint pial supply on the preoperative angiogram, although the microscopic view during the operation identified the pial supply (patient no. 6). Fusion imaging with DSA and MRI might reinforce the differential diagnosis for these two types. If the fusion image, however, is not available, an oblique view on a vertebral angiogram should be taken to identify the gap showing a short distance between the fistulous point and the medial aspect of the ipsilateral VA. Both RAVFs in patients were found to have this finding, but no DAVF patients did. This finding may be useful to suggest the differential diagnosis of RAVF or DAVF at the C1 level on a routine angiogram.

On the other hand, EDAVFs mainly affect the lumbar level. They typically form a shunt in the narrow space between the ventral dura and the dorsal vertebral body, arising mostly from the dorsal somatic branch of a segmental artery, with drainage to a radiculomeningeal vein.[10] Those with intradural drainage have a high risk of ominous symptoms, whereas those without intradural drainage follow an unknown clinical course. In the present study, the three patients with six EDAVFs did not undergo any treatment because the shunt flow was relatively low grade without intradural venous reflux or spinal cord compression. Thus, all of them obtained spontaneous regression within 2–10 months. Compared with a lumbar lesion, the pressure of the cervical venous plexus varies with intracranial pressure and head position because of gravity. When lying or sleeping, the head level is the same as the heart level, although when standing or sitting, the head is higher than the heart. If the flow volume is not very high, the fistula may disappear spontaneously due to increased venous pressure.

Thinking of the gravity effect, intradural venous reflux arising from an EDAVF hardly occurs in the upper cervical region because the AVF is located at a higher level than the heart level in daily life, even after the formation of the AVF. That may be associated with the fact that all six EDAVFs never had intradural venous reflux, but EDAVFs in the lumbar spine often had reflux. Given this background, we would like to recommend aggressive treatment when CCJ-EDAVF patients have intradural drainage, marked venous congestion, or a concomitant pial feeder aneurysm.[4,25,44] However, conservative observation by serial imaging would be recommended as the first choice for such patients without any of the risk factors. Since small EDAVFs are not always detected by MRI or CTA, the actual number of patients is assumed to be underestimated. More patients need to be studied in the future.

Multiplicity and etiology

It is said that venous hypertension may contribute to the genesis of these AVFs. As described above, venous pressure in the upper cervical level should be lower because of gravity in the daytime. However, a bed-ridden condition for a long time resulting from SAH with high intracranial pressure is assumed to lead to an increase in paravertebral venous pressure, thereby forming *de novo* AVFs. In fact, 4 of 11 patients with 7 of 14 lesions were incidentally found during examination for SAH relevant to a cerebral aneurysm or intracranial AV shunt.

Regarding comorbidities, the present cohort included five patients with various other AV shunt diseases, including a cerebellar AVM in one, intracranial DAVFs in two, and multiple CCJAVFs in two. The high incidence of multiple AV shunts may be attributed to venous hypertension affected by the formation of the primary AVM or other DAVF. Several authors documented the heterogeneous multiplicity, such as a CCJAVF with a soft-tissue AVF in the same metamere,[2] spinal pial AVF, cerebellar pial AVM, intracranial DAVF, contralateral spinal DAVF,[8] etc. Homogeneous multiple CCJAVFs have also been reported by some authors.[6,23,29] If a certain AV shunt disease occurs and starts to cause venous hypertension or venous thrombosis in the craniocervical junction, a secondary CCJAVF might be formed by the molecular biological mechanism described below.

In addition, minor trauma may be associated with the formation of AVFs. There is a special structure between the C1 and the C2 vertebra with the atlanto-axial joint facilitating the movement of wide neck rotation. It may affect the spinal nerve or VA due to repeated minor trauma in daily life, exercise, or sports, especially at the C1/C2 level, resulting in the genesis of a micro-AV shunt. This mechanism could be relevant to the frequency of *de novo* AVFs at the C1–C2 level, whereas it is less frequent at the thoracic spine level.

Development of RAVF and neurovascular wiring

However, the question of how we explain the hypothesis in which the spinal nerve plays a role in navigating an AVF must be considered. According to the literature, the neuronal network and blood vessel network interact with each other and are termed "neurovascular wiring," "neurovascular link," or "neurovascular congruence."[3,43] These two systems are responsible for transfer of oxygen, nutrients, and information and thereby constitute highly important communication systems in higher organisms.[42] Although this concept was already illustrated by Andreas Vesalius in the 16th century,[3,27] the physiological function at the molecular level remains unknown. Recent genetic studies have shown that vessels and nerves share many common principles and signals for navigation, proliferation, and survival.[43] For instance, Mukouyama found that sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin.[19] Li *et al.* identified

CXCL12 as a critical factor secreted by the nerve that initiates the process of cutaneous vascular remodeling.[16] Moreover, recent research showed that the vascular endothelial growth factor (VEGF) receptor, VEGFR2, which is a key regulator of angiogenesis, is more abundant in neuronal cells than in endothelial cells in developing mouse retinae. Neuronal-specific knockout of VEGFR2 in retinae of mice does not affect neuronal development, but causes vessels to branch vertically into the neuronal layers. These results suggest a new molecular system in which neurons control the concentration of VEGF by taking up this factor to regulate angiogenesis.[22]

These new findings from academic research seem to be consistent with the theory that an AVF occurs adjacent to the nerve root at the CCJ level, as previously documented in a domestic, multicenter study.[4] There may also be an association between such a molecular system and the genesis of the nonsinus type of DAVF, such as a spinal AVF in the vicinity of the spinal nerve root sleeve, an anterior cranial fossa DAVF in the vicinity of the olfactory nerve, and an anterior condylar confluence DAVF in the vicinity of the hypoglossal nerve. To date, several reports describing the occurrence of DAVFs affected by basic fibroblast growth factor, VEGF, and venous hypertension have been published.[13-15,37-39] Several authors have also documented that sinus thrombosis or cerebral vein thrombosis may precede an AV shunt.[5,17,24] Another theory proposes that hypoxia promotes angiogenesis, thereby initiating an AV shunt.[29,30] The pathogenesis of DAVF has been established by the concept that a DAVF generally occurs on the dura mater or venous sinus. However, neurons may be another important factor that induces the genesis of AV shunts.

Study limitations

The present study has several limitations. First, the study design was a single-center, retrospective approach. Second, only 11 patients managed at our institution during the 14-year period were analyzed. The total number of patients was not enough to demonstrate the validity of our theory. Third, surgical confirmation of the shunt point was not performed in all patients. This rare, unique, and angiographically complicated disease requires a multicenter, prospective study to carefully establish its etiology and the optimal management.

CONCLUSION

CCJAVFs have many variations, such as in shunting site, angioarchitecture, and multiplicity, and they were frequently associated with coincidental vascular lesions. For symptomatic DAVF and RAVF lesions with intradural drainage, surgical disconnection is preferred, whereas asymptomatic EDAVFs without dangerous drainage may regress spontaneously on serial imaging.

Declaration of patient consent

Institutional Review Board (IRB) permission was obtained for this study.

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Conflicts of interest

There are no conflicts of interest.

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