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Clinical features, treatment strategies and outcomes of craniocervical junction arteriovenous fistulas: a cohort study of 193 patients

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ABSTRACT

Background Craniocervical junction (CCJ) arteriovenous fistulas (AVFs) are rare. The current treatment strategies for AVFs with different angioarchitecture need to be clarified. The present study aimed to analyse the correlation between angioarchitecture and clinical characteristics, share our experience in treating this disease and identify risk factors associated with subarachnoid haemorrhage (SAH) and poor outcomes.

Methods A total of 198 consecutive patients with CCJ AVFs from our neurosurgical centre were retrospectively reviewed. The patients were grouped according to their clinical manifestations, and their baseline clinical characteristics, angioarchitecture, treatment strategies and outcomes were summarised.

Results The patients' median age was 56 years (IQR 47–62 years). The majority of patients were men with 166 (83.8%) patients. The most common clinical manifestation was SAH (52.0%), followed by venous hypertensive myelopathy (VHM) (45.5%). The most common CCJ AVFs type was dural AVF, with 132 (63.5%) fistulas. The most frequent fistula location was C-1 (68.7%) and dural branch of vertebral artery (70.2%) was the most involved arterial feeders for fistulas. The most common direction of venous drainage was descending intradural drainage (40.9%), followed by ascending intradural drainage (36.5%). Microsurgery was the most common treatment strategy applied for 151 (76.3%) patients, 15 (7.6%) patients were treated with interventional embolisation only, and 27 (13.6%) received both interventional embolisation and microsurgical treatment. The learning curve for microsurgery only was analysed by cumulative summation method, and the turning point was the 70th case, and blood loss in post-group was lower than that in pre-group (p=0.034). At the last follow-up, there were 155 (78.3%) patients with favourable outcomes (modified Rankin Scale(mRS)<3). Age≥56 (OR 2.038, 95% CI 1.039 to 3.998, p=0.038), VHM as the clinical manifestation (OR 4.102, 95% CI 2.108 to 7.982, p<0.001) and pretreatment mRS≥3 (OR 3.127, 95% CI 1.617 to 6.047, p<0.001) were significantly associated with poor outcomes.

Conclusion The arterial feeders and direction of the venous drainage were important factors in the clinical presentations. The location of fistula and drainage vein was essential for choosing different treatment strategies. Older age, VHM onset and poor pretreatment functional status predicted poor outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The key points of different treatment strategies for craniocervical junction (CCJ) arteriovenous fistulas (AVFs) are not currently elaborated.

WHAT THIS STUDY ADDS

⇒ This study shares treatment experience of CCJ AVFs and identify risk factors associated with subarachnoid haemorrhage and poor outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study allows peers to learn more about angioarchitecture of CCJ AVFs and help treat them.

INTRODUCTION

The craniocervical junction (CCJ), known as a craniovertebral junction that usually represents the occipital bone, condyles, the atlas and the axis, has complex and unique vascular and bone anatomy.[1] Arteriovenous fistulas (AVFs) at this region were quite different from other regions of spinal AVFs in terms of clinical characteristics, angioarchitecture, treatment modalities and outcomes. Moreover, the incidence rate of CCJ AVFs was low, accounting for about 2% of spinal vascular malformations.[2–6] However, previous studies often reported only a small number of cases, which were not enough to fully interpret CCJ AVF. In this study, we retrospectively analysed CCJ AVF patients treated at our neurosurgical centre in the past 20 years (from 2002 to 2021) and analysed them according to their clinical presentations. To the best of our knowledge, this is the largest retrospective study of patients with CCJ AVF.

METHODS

Patients and follow-up

This retrospective study included 198 patients with CCJ AVFs (a total of 208 CCJ AVFs) treated at our institution between January

2002 and December 2021. Clinical and radiological data were collected from patients. Subarachnoid haemorrhage (SAH) was confirmed by CT scanning of the head. For patients with SAH. Hunt and Hess grading system[7] was also used for patients with SAH to evaluate their condition. Venous hypertensive myelopathy (VHM) was defined as spinal cord oedema and neurological dysfunction due to increased spinal venous pressure, which could present with motor and sensory dysfunction. All AVFs were confirmed by digital subtraction angiography (DSA). In addition to conservative treatment, treatment modalities included microsurgery and interventional embolisation alone or combined. Intraoperative or postoperative angiography and intraoperative indocyanine green (ICG) angiography were used to confirm obliteration of the fistula. Recurrence was defined as fistula recurrence or a new fistula formation diagnosis by DSA after curative interventional embolisation or microsurgery. For those AVFs treated by microsurgery alone, we explored the learning curve of microsurgical treatment of CCJ AVFs by the cumulative summation (CUSUM) method.[8]

According to DSA and intraoperative sighting, each patient was diagnosed by two surgeons (neurosurgeons and neurointerventionalists with 20 years of experience in the field). Hiramatsu *et al*[5] classification method was used with few modifications. According to our definition, the location of arteriovenous shunt was the standard of classification. Paravertebral AVF (PVAVF) was defined as the abnormal connection between arteries and paravertebral venous plexus outside spinal canal; dural AVF (DAVF) was defined as the arteriovenous shunt located on the dural mater; radicular AVF (RAVF) was defined as the arteriovenous shunt located on the spinal nerve roots; epidural AVF (EDAVF) was defined as the arteriovenous shunt located on the surface of the dura mater; perimedullary AVF (PAVF) was defined as the arteriovenous shunt located on the surface of the spinal cord. Schematic illustrations were used to show different AVFs (figure 1).

Follow-up was performed by clinical examination or telephone interview. There were 169 (85.4%) patients with at least 3-month follow-up, while a total of 151 patients have been followed up to now; and the median follow-up time was 31.5 months.

Statistical analysis

SPSS V.24.0 software was used for statistical analysis. The χ^2 test and the Fisher exact test were used to compare categorical variables of two groups, and Wilcoxon signed-rank test was used to compare ages and outcomes (mRS scores). Baseline patient characteristics, angiographic findings and AVF types were assessed for association with SAH. Baseline patient characteristics, angiographic findings, AVF types, treatment modalities, complications and recurrence were assessed for association with post-treatment mRS≥3. The results are presented as relative risk with 95% CIs. The potential risk factors with p<0.10 in univariate analysis were included as confounders in the multivariate logistic regression model for multivariate

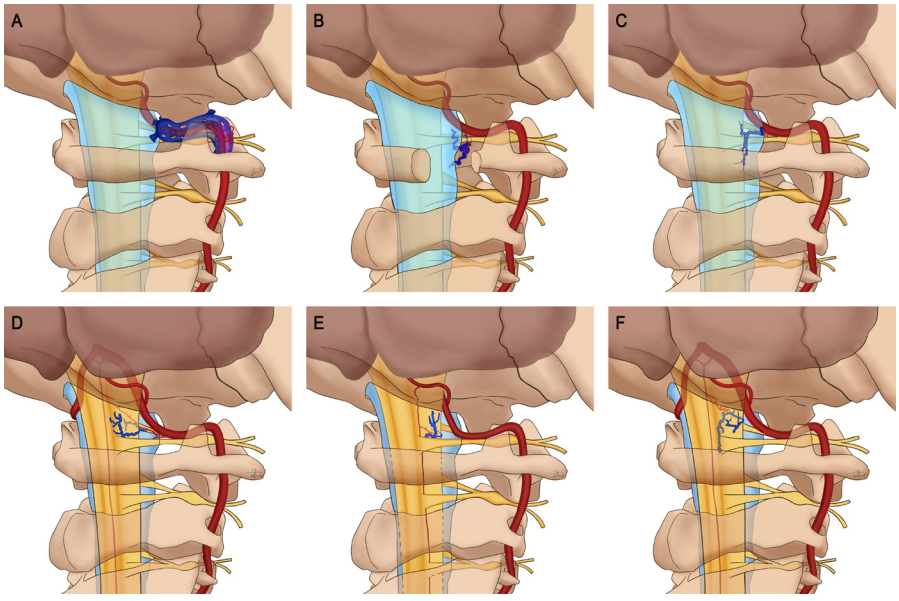

Figure 1 Schematic illustrations of craniocervical junction arteriovenous fistulas (AVFs). Posteroanterior angiographic diagram of paravertebral AVF (A). This AVF is fed by vertebral artery, drains into the paravertebral venous plexus. Posteroanterior angiographic diagram of epidural AVF (B). This AVF is fed by dural branch of vertebral artery (DBVA), drains into the epidural veins and the shunt is located outside the dura mater. Posteroanterior angiographic diagram of dural AVF (C). This AVF is fed by DBVA, drains into the intradural veins and the shunt is located on the dural mater. Posteroanterior angiographic diagram of radicular AVF (D). This AVF is fed by anterior spinal artery (ASA) and RA, drains into the intradural veins and the shunt is located on the spinal nerve roots. Posteroanterior angiographic diagram of perimedullary AVF (E,F). One AVF is fed by lateral spinal artery (E), the other AVF is fed by ASA (F). Both AVFs drain into the intradural veins and shunts are located on the surface of the spinal cord. Copyright Jiachen Wang Published with permission.

Table 1 Summary of clinical and angiographic characteristics, treatment modality

	N
Total no. of patients (lesions)	198 (208)
Median age in years (IQR)	56 (47–62)
Male/female	166 (83.8)/32 (16.2)
Presentation	
Subarachnoid haemorrhage	103 (52.0)
Venous hypertensive myelopathy	90 (45.5)
Tinnitus	2 (1.0)
Cranial nerve paralysis	3 (1.5)
Steroid administration	24 (12.1)
Side	
Left	95 (45.7)
Right	107 (51.4)
Both	6 (2.9)
Arteriovenous fistula types	
Paravertebral arteriovenous fistula	3 (1.4)
Epidural AVF	19 (9.1)
Paravertebral AVF	15 (7.2)
Radicular AVF	39 (18.8)
Dural AVF	132 (63.5)
Fistula location	
Foramen magnum	22 (10.6)
C-1	143 (68.7)
C-2	43 (20.7)
Arterial feeders	
Dural branch of vertebral artery	139 (70.2)
RA	38 (19.2)
Anterior spinal artery	32 (16.2)
Lateral spinal artery	20 (10.1)
PICA	5 (2.5)
APA	22 (11.1)
OA	9 (4.5)
PMA	5 (2.5)
MMA	1 (0.5)
Direction of the venous drainage	
Ascending intradural	77 (36.5)
Descending intradural	87 (40.9)
Bidirectional intradural	23 (12.0)
Epidural	18 (9.1)
Paravertebral venous plexus	3 (1.4)
Aneurysmal structure	60 (30.3)
Varix	135 (68.2)
Treatment	
Conservative	5 (2.5)
Surgery	151 (76.3)
Embolisation	15 (7.6)
Embolisation+surgery	27 (13.6)

Values are shown as the number (%)of patients or lesions, unless indicated otherwise.
APA, ascending pharyngeal artery; AVF, arteriovenous fistula; C, cervical; MMA, middle meningeal artery; OA, occipital artery; PICA, posterior inferior cerebellar artery; PMA, posterior meningeal artery; RA, radicular arter.

analysis to determine whether they were risk factors. The final model variables were selected using the forward conditional method. The results were presented as ORs with 95% CIs. Statistical analyses were two-sided, and p<0.05 indicated statistical significance.

The learning curve was analysed by CUSUM method. The formula is as follows: CUSUM= $\sum_{i=1}^{n}(Xi-\mu)$, where Xi indicates the actual microsurgical time for each patient and μ indicates the average microsurgical time of patients. The difference between the microsurgical time of each patient in chronological order and the average microsurgical time of the whole group was summed and the learning curve was obtained.

RESULTS

Clinical characteristics

Table 1 describes the basic information of patients in this study, and patients were grouped according to onset, online supplemental table 1 describes the clinical characteristics of patients. As almost all patients in this study presented with SAH or VHM, we also compared the data of the two groups; the results were shown in the table 2. There were 166 (83.8%) male patients, and the median age (IQR) was 56 (47–62) years. Patients with VHM were older than those with SAH (p<0.001). Among 198 patients, SAH was the main clinical manifestation, which occurred in 103 (52.0%) cases. VHM was the second most common onset mode, found in 90 (45.5%) cases. Of those patients who presented with SAH, 99 (96.1%) patients had with a mild neurologic condition grade (Hunt and Hess grade 1–3), and 4 (3.9%) had a severe neurologic condition (Hunt and Hess grade 4 or 5). Among 24 (26.7%) patients with VHM who were misdiagnosed and treated with steroids in other hospitals, symptoms worsened in 21 of these patients after steroid administration.

Angioarchitecture

Online supplemental table 2 listed the information on angioarchitecture in different groups. A total of 188 patients had a single fistula and 10 had dual fistulas. The most common CCJ AVFs type was DAVF, with 132 (63.5%) fistulas. The remaining types of AVFs, in descending order of the number of patients, were: RAVF, EDAVF, PAVF

Table 2 Comparison of patients' data between SAH and VHM groups

	SAH	VHM	Total	P value
Patients, n	103 (52.0)	90 (45.5)	193	
Lesions, n	113 (54.3)	90 (43.3)	203	
Male sex	82 (79.6)	79 (87.8)	161 (83.4)	0.184
Median age (IQR)	52 (46–60)	59 (51–65)	56 (47–63)	**<0.001**
Pretreatment mRS				0.150
1	27 (26.2)	24 (26.7)	51 (26.4)	
2	41 (39.8)	22 (24.4)	63 (32.6)	
3	13 (12.6)	11 (12.2)	24 (12.4)	
4	7 (6.8)	15 (16.7)	22 (11.4)	
5	15 (14.6)	18 (20.0)	33 (17.1)	
AVF type				**<0.001**
PMAVF	1 (0.9)	1 (1.1)	2 (1.0)	1.000
Epidural AVF	14 (12.4)	4 (4.4)	18 (8.9)	**0.048**
Paravertebral AVF	13 (11.5)	2 (2.2)	15 (7.4)	**0.012**
Radicular AVF	29 (25.7)	10 (11.1)	39 (19.2)	**0.009**
Dural AVF	56 (49.6)	73 (81.1)	129 (63.5)	**<0.001**
Side				0.422
Left	50 (44.2)	43 (47.8)	93 (45.8)	
Right	61 (54.0)	43 (47.8)	104 (51.2)	
Both	2 (1.8)	4 (4.2)	6 (3.0)	
Fistula location				**0.007**
Foramen magnum	6 (5.3)	15 (16.7)	21 (10.3)	**0.008**
C-1	78 (69.0)	63 (70.0)	141 (69.5)	0.881
C-2	29 (25.7)	12 (13.3)	41 (20.2)	**0.030**
Arterial feeders				**<0.001**
Dural branch of vertebral artery	64 (62.1)	70 (77.8)	134 (66.0)	**0.019**
Radicular artery	28 (27.2)	10 (11.1)	38 (18.7)	**0.005**
Anterior spinal artery	27 (26.2)	5 (5.6)	32 (15.8)	**<0.001**
Lateral spinal artery	16 (15.5)	4 (4.4)	20 (9.9)	**0.012**
Posterior inferior cerebellar artery	3 (2.9)	2 (2.2)	5 (2.5)	1.000
Ascending pharyngeal artery	6 (5.8)	14 (15.6)	20 (9.9)	**0.027**
Occipital artery	2 (1.9)	6 (6.7)	8 (3.9)	0.200
Posterior meningeal artery	4 (3.9)	1 (1.1)	5 (2.5)	0.450
Middle meningeal artery	0 (0.0)	1 (1.1)	1 (0.5)	0.466
Direction of the venous drainage				**<0.001**
Ascending intradural	69 (61.1)	6 (6.7)	75 (36.9)	**<0.001**
Descending intradural	14 (12.4)	70 (77.8)	84 (41.4)	**<0.001**
Bidirectional intradural	14 (12.4)	10 (11.1)	24 (11.8)	0.779
Epidural	16 (14.2)	2 (2.2)	18 (8.9)	**0.003**
Paravertebral venous plexus	0 (0.0)	2 (2.2)	2 (1.0)	0.195
Aneurysmal structure	47 (45.6)	13 (14.4)	60 (29.6)	**<0.001**
Varix	66 (64.1)	66 (73.3)	132 (65.0)	0.168
Treatment				0.351
Conservative	3 (2.9)	1 (1.1)	4 (2.0)	
Surgery	76 (73.8)	73 (81.1)	149 (73.4)	

Continued

Table 2 Continued

	SAH	VHM	Total	P value
Embolisation	6 (5.8)	7 (7.8)	13 (6.4)	
Embolisation+surgery	18 (17.5)	9 (10.0)	27 (13.3)	
Complications	20 (19.4)	14 (15.6)	34 (16.7)	0.482
Recurrence	3 (2.9)	5 (4.4)	8 (3.9)	0.578
Post-treatment modified Rankin Scale (mRS)*				**<0.001**
0	49 (47.6)	14 (15.6)	63 (31.0)	
1	46 (44.7)	30 (33.3)	76 (37.4)	
2	1 (1.0)	10 (11.1)	11 (5.4)	
3	1 (1.0)	12 (13.3)	13 (6.4)	
4	3 (2.9)	11 (12.2)	14 (6.9)	
5	0 (0.0)	5 (5.6)	5 (2.5)	
6	3 (2.9)	8 (8.9)	11 (5.4)	

Values are shown as the number (%) of patients or lesions, unless indicated otherwise.
*Post-treatment mRS was evaluated according to the last follow-up.
AVF, arteriovenous fistula; C, cervical; SAH, subarachnoid haemorrhage; VHM, venous hypertensive myelopathy.

and PVAVF. Compared with patients with VHM, patients with SAH had a higher proportion of EDAVF, PAVF and RAVF (p=0.048, p=0.012 and p=0.009, respectively), while patients with VHM were more likely to suffer from DAVF (p<0.001).

There were 95 (45.7%) fistulas located on the left side, 107 (51.4%) fistulas on the right side and 6 (2.9%) fistulas fed by both side arteries. The most common fistula location in CCJ AVFs was C-1 level, with 143 (68.7%) located at the C-1 level. In the VHM group, the probability of the

Table 3 Risk factors associated with subarachnoid haemorrhage*

	Univariate			Multivariate		
Variable	RR	95% CI	P value	OR	95% CI	P value
Age<56	1.509	1.150 to 1.979	**0.002**			
Epidural AVF	1.465	1.080 to 1.989	0.052			
Perimedullary AVF	1.898	1.554 to 2.318	**<0.001**			
Radicular AVF	1.551	1.208 to 1.992	**0.004**			
Dural AVF	0.83	0.455 to 0.747	**<0.001**			
Fistula location: foramen magnum	0.490	0.244 to 0.981	**0.012**			
Fistula location: C-2	1.343	1.023 to 1.763	0.055			
Arterial feeder: dural branch of vertebral artery	0.679	0.528 to 0.873	**0.005**	0.334	0.146 to 0.766	**0.010**
Arterial feeder: Radicular artery	1.551	1.208 to 1.992	**0.004**			
Arterial feeder: anterior spinal artery	1.819	1.458 to 2.270	**<0.001**			
Arterial feeder: lateral spinal artery	1.739	1.371 to 2.206	**0.002**			
Arterial feeder: Ascending pharyngeal artery	0.490	0.244 to 0.981	**0.012**			
Drain: ascending intradural drainage	3.796	2.572 to 5.603	**<0.001**	11.096	4.856 to 25.356	**<0.001**
Drain: descending intradural drainage	0.301	0.216 to 0.419	**<0.001**	0.222	0.112 to 0.441	**<0.001**
Drain: epidural drainage	1.713	1.341 to 2.189	**0.004**	11.099	2.429 to 50.720	**0.002**
Aneurysmal structure	1.971	1.553 to 2.502	**<0.001**	2.807	1.102 to 7.149	**0.031**

*List only options with p<0.100.
AVF, arteriovenous fistula; C, cervical; RR, relative risk.

Table 4 Risk factors associated with post-treatment mRS≥3*

	Univariate			Multivariate		
Variable	RR	95% CI	P value	OR	95% CI	P value
Age≥56	2.335	1.275 to 4.277	**0.003**	2.038	1.039 to 3.998	**0.038**
Presentation: subarachnoid haemorrhage	0.176	0.082 to 0.376	**<0.001**			
Presentation: venous hypertensive myelopathy	6.171	2.887 to 13.193	**<0.001**	4.102	2.108 to 7.982	**<0.001**
Steroid administration	2.806	1.682 to 4.682	**<0.001**			
Pretreatment mRS≥3	4.971	2.601 to 9.501	**<0.001**	3.127	1.617 to 6.047	**<0.001**
Dural arteriovenous fistula	1.889	0.964 to 3.701	0.051			
Fistula location: C-2	0.393	0.149 to 1.036	**0.037**			
Arterial feeder: anterior spinal artery	0.389	0.128 to 1.181	0.064			
Drain: ascending intradural drainage	0.330	0.177 to 0.617	**<0.001**			
Drain: descending intradural drainage	3.572	1.747 to 7.304	**<0.001**			
Aneurysmal structure	0.447	0.211 to 0.947	**0.024**			
Varix	1.763	0.901 to 3.449	0.083			

*List only options with p<0.100.
C, cervical; mRS, modified Rankin Scale; RR, relative risk.

fistula located in the FM was slightly higher (p=0.008), and the probability of the fistula located in C-2 was slightly lower (p=0.030).

The most common arterial feeders of CCJ AVFs were DBVA, with 139 (70.2%) fistulas fed by DBVA. The next most common arterial feeders were radicular artery (RA), with 38 (19.2%) fistulas. In SAH group, the proportions of RA, anterior spinal artery (ASA) and lateral spinal artery (LSA) as arterial feeders were significantly higher (p=0.005, p<0.001 and p=0.012, respectively). However, in the VHM group, the proportion of DBVA and APA was higher (p=0.019 and p=0.027).

Intradural drainage was the most common direction of venous drainage in CCJ AVFs. All PVAVFs drained into the paravertebral venous plexus. Comparison of angioarchitecture of the two groups of patients with SAH or VHM revealed a significant relationship between the directions of venous drainage and in the clinical presentations (p<0.001). There were greater proportion of ascending intradural drainage and epidural drainage in SAH group (p<0.001 and p=0.003), whereas descending intradural drainage was more common in VHM group (p<0.001). Aneurysmal structures occurred in 60 (30.3%) patients, while patients with SAH were more prone to aneurysmal structures (p<0.001). Varices were presented on the venous drainage in 135 (68.2%) patients.

Treatment and outcomes

The treatment modalities and outcomes of patients in this study were listed in online supplemental table 3. A total of 193 (97.5%) patients underwent invasive intervention. Microsurgery was the most common treatment strategy and was used for the treatment of 151 (76.3%) patients, while 15 (7.6%) patients only underwent interventional embolisation and 27 (13.6%) received both interventional embolisation and microsurgical treatment. In total, 5 (2.5%) patients treated with conservative treatment were in good condition at the last follow-up, and none showed any aggravation of symptoms.

A total of 34 (17.2%) patients experienced complications after surgical intervention, of which the most common complication was infection include 17 (8.6%) intracranial infection and 3 (1.5%) pulmonary infection, followed by cerebrospinal fluid leak, with 4 (2.0%) patients. One (0.5%) patient underwent decompressive craniectomy due to cerebral infarction and recovered well. Two (1.0%) patients died of intractable infection, one with intracranial infection and the other with pulmonary infection. Other patients with complications did not leave permanent dysfunction. Among eight (4.0%) patients with recurrence of AVF confirmed on DSA review at 3 or 6 months after treatment who underwent secondary invasive intervention, of which six patients received secondary surgical intervention and two opted for conservative treatment.

For the overall patient, the median mRS Score of post-treatment was 1 at the last follow-up. The patient's function was improved after surgical intervention (p<0.001). There were 155 (78.3%) patients with favourable outcomes (mRS<3). In addition, patients with SAH had better postoperative functional recovery than patients with VHM (p<0.001).

The results of the CUSUM method in online supplemental figure 2 showed that the curve reached a maximum in the 70th case and then gradually decreases. Therefore, the turning point of the learning curve was chosen as the 70th case. According to the turning point, the curve could be divided into pre-group and post-group in chronological order. Comparison of clinical

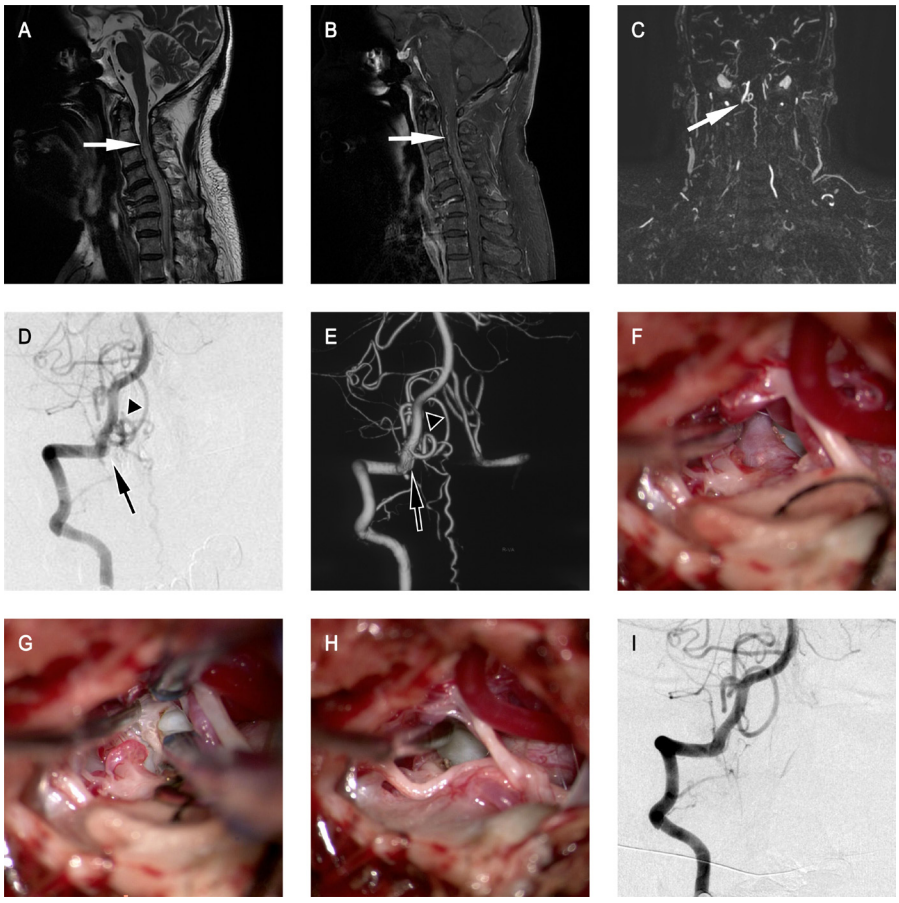

Figure 2 This male dural arteriovenous fistula (AVF) patient presented with venous hypertensive myelopathy who was treated with microsurgery. The T2-weighted sagittal MRI image (A) showed high signal intensities of cervical cord and flow-void sign (white arrow in A). The enhanced sagittal MRI image (B) showed abnormal vascular dilatation on the ventral cervical cord (white arrow in B). The 4D MRI image (C) showed abnormal vascular dilatation originating from the right vertebral artery (VA) (white arrow in C). Preoperative angiography of right VA (D,E). The AVF was fed by right C-1 dural branch of vertebral artery (black arrow in D,E), the feeder drains into the intradural vein (black arrowhead in D,E). Intraoperative image showed dilated drainage vein (F). Intraoperative image showed the electrocoagulation of the drainage vein (G). Intraoperative image showed the disconnection of the AVF (H). Postoperative angiography of right VA (I) 7 days after microsurgery.

characteristics, microsurgical procedures and outcomes between two groups (online supplemental table 4): there was no significant difference between the two groups in terms of clinical characteristics and outcomes (p>0.05). There were shorter microsurgical time and less blood loss in post-group (p=0.009 and p=0.034).

Risk factors

Due to the rapid onset of SAH and poor postoperative functional recovery of some patients, we also analysed the risk factors. Risk factors associated with SAH are presented in table 3 and risk factors associated with post-treatment mRS≥3 are presented in table 4. After multivariate analysis, DBVA as an arterial feeder (OR 0.334, 95% CI 0.146 to 0.766, p=0.010), ascending intradural drainage (OR 11.096, 95% CI 4.856 to 25.356, p<0.001), descending intradural drainage (OR 0.222, 95% CI 0.112 to 0.441, p<0.001), epidural drainage (OR 11.099, 95% CI 2.429 to 50.720, p=0.002) and aneurysmal structure (OR 2.807, 95% CI 1.102 to 7.149, p=0.031) were found to be significantly associated with SAH. Age≥56 (OR 2.038, 95% CI 1.039 to 3.998, p=0.038), VHM as the clinical manifestation (OR 4.102, 95% CI 2.108 to 7.982, p<0.001) and pretreatment mRS≥3 (OR 3.127, 95% CI 1.617 to 6.047, p<0.001) were significantly associated with poor outcomes.

DISCUSSION

CCJ AVFs are not as common as spinal AVFs in other regions. In the early years, most of the literature on this disease were case or cases reports.[9–14] In the last decade, an increasing number of literature reviews,[4 15 16] single-centre studies[17–19] or multicentre studies[5 20 21] have been published to, thus furthering our understanding of CCJ AVFs. However, there are still some issues that should be further explored. In the present study, we further analysed the mode of onset, angioarchitecture, treatment strategies and outcomes of this disease based on 20 years of data from our centre. To the best of our knowledge, this was the largest CCJ AVF data used in the research thus far.

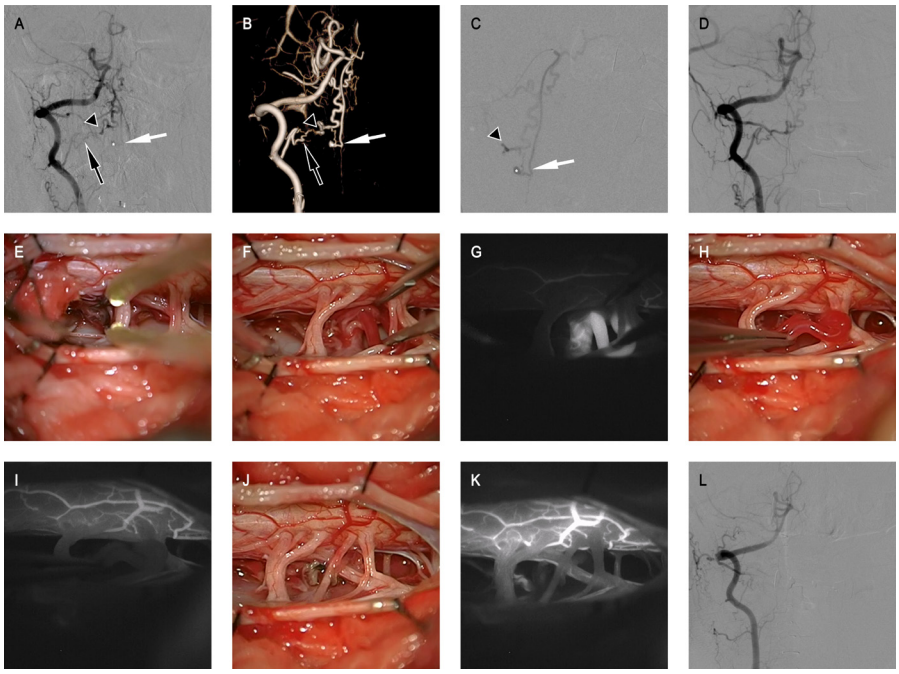

Figure 3 This male radicular arteriovenous fistula (AVF) patient presented with venous hypertensive myelopathy who was treated with interventional embolisation and microsurgery. Preoperative angiography of right vertebral artery (VA) (A,B). Superselective angiography of anterior spinal artery (ASA) (C). The AVF was fed by right C-2 RA (black arrow in A,B) and ASA (white arrow in A–C), the feeder drains into the intradural vein (black arrowhead in A–C). The ASA formed an aneurysmal structure (white asterisk in A–C). Postembolisation angiography of right VA (D). Intraoperative image showed the aneurysmal structure after embolisation (E). Intraoperative image and intraoperative indocyanine green (ICG) fluorescence angiography showed the AVF and the draining vein (F,G). Intraoperative image and ICG fluorescence angiography showed occlusion test to identify the draining vein (H,I). Intraoperative image and ICG fluorescence angiography showed the disconnection of the AVF (J,K). Postoperative angiography of right VA (L) 4 days after microsurgery.

Clinical characteristics and angioarchitecture

SDAVF usually occurred in middle-aged people, with obvious gender differences (male:female ratio, 6:1).[6] Previous studies have also reported that CCJ AVFs have a male prevalence with a male-to-female ratio of about 3:1.[4 15] Moreover, the existing literature identified gender as a relevant factor affecting angioarchitecture. The proportion of males in patients with spinal arterial feeders was higher (p=0.002).[22] In this study, the proportion of men and women was about 5:1, which could be due to the high number of patients with spinal arterial feeders. Although CCJ AVF tended to occur in middle-aged people, patients with VHM were older (p<0.001), which could be due to the insidious onset and longer duration of the disease, resulting in misdiagnosis in many patients.

The initial presentation of VHM was mostly numbness or weakness of the limbs. And in the early stage of the disease, the spinal cord sagittal T2 MRI mostly showed high signal, with less flow-void sign, making it difficult to differentiate from myelitis in terms of symptoms and images. In our experience, the use of enhanced MRI or 4D MRI could more clearly show the large drainage veins, thus helping to identify the location of fistula (figure 2). However, many patients were still misdiagnosed and received steroid administration due to difficulties in differential diagnosis in other hospitals. For spinal DAVF, steroid administration often aggravated the disease, leading to more dangerous outcomes when the lesion was located in the CCJ.[23 24] Among the patients with VHM in the present study, 24 (12.1%) patients had received steroid administration, 9 of whom developed high paraplegia immediately and 3 developed medullary oedema with respiratory failure. These unfortunate outcomes suggest that more caution should be taken when administering steroids to patients suspected of CCJ AVFs. Similarly, there were three patients with tinnitus and two patients with facial palsy. Both of these conditions are uncommon clinical manifestations that should also be noted.

As a common clinical manifestation of CCJ AVFs, SAH was the most common clinical manifestation in the present study, which is in line with the previous literature.[5 21] SAH had a rapid onset and could lead to consciousness disorder, In this study, 99 (96.1%) patients had a mild neurologic condition grade, while some only presented with neck discomfort. This could be because a small vein rupture causes SAH of CCJ AVF. In previous studies, clinical manifestations were significantly related to angioarchitecture, especially the direction of venous drainage.[4 5 10 11 15] Our univariate analysis revealed that AVF types, arterial feeders and direction of the venous drainage in the SAH group were significantly different from those in the non-SAH group. Also, multivariate

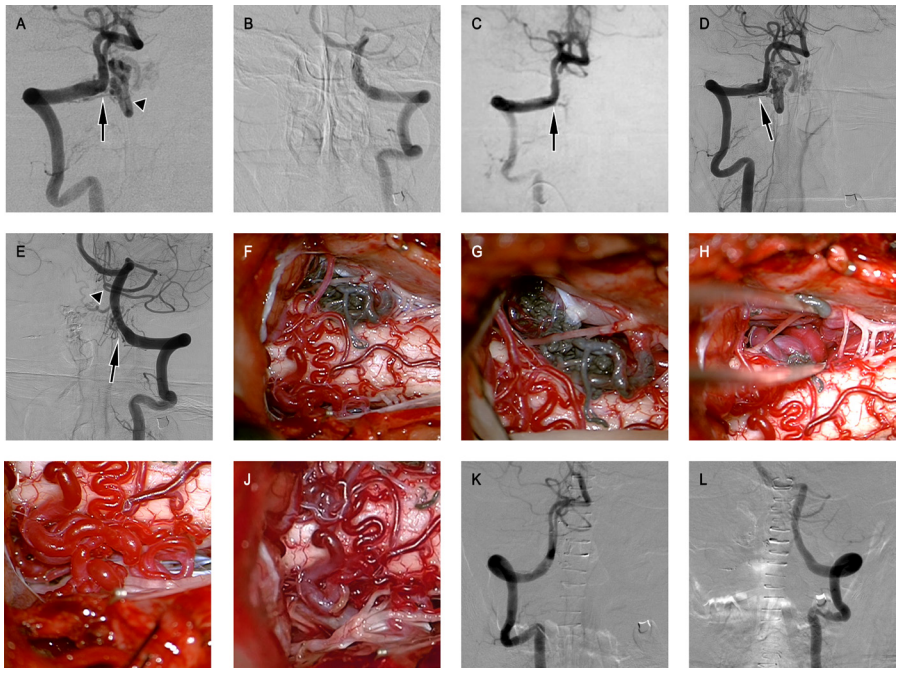

Figure 4 This male dural arteriovenous fistula (AVF) patient presented with venous hypertensive myelopathy who was treated with interventional embolisation and microsurgery. Preoperative angiography of right vertebral artery (VA) (A) and left VA (B) before interventional embolisation in external hospital. The AVF was fed by right C-1 dural branch of vertebral artery (DBVA) (black arrow in A), the feeder drains into the intradural vein (black arrowhead in A). Angiography of right VA (C) 4 months after interventional embolisation showed partial recanalisation of AVF (black arrow in C). Angiography of right VA (D) and left VA (E) 8 months after interventional embolisation. Right AVF had recanalised (black arrow in D). There was a newly formed AVF on the left which was fed by left C-1 DBVA (black arrow in E), the feeder drains into the intradural vein (black arrowhead in E). Intraoperative image showed bilateral AVFs and draining veins (F). Intraoperative image showed right AVF, the draining vein (G) and the disconnection of the AVF (H). Intraoperative image showed left AVF, the draining vein (I) and the disconnection of the AVF (J). Postoperative angiography of right VA (K) and left VA (L) 4 days after microsurgery.

analysis revealed that ascending intradural drainage, epidural drainage and aneurysmal structure were risk factors for SAH. We speculated that when reflux occurred in the draining vein, the venous pressure increased more significantly, thus increasing the risk of rupture and bleeding.

Treatment

Microsurgery and interventional embolisation are optional treatment strategies for CCJ AVFs. However, previous studies have shown that microsurgery was the favoured treatment option for CCJ AVF, which usually leaded in better outcomes and less retreatments.[4 21] According to the treatment experience at our centre, microsurgery could be used as the first choice for CCJ AVF, while the angioarchitecture of AVF is also essential for our treatment strategies.

For fistulas with a relatively simple angioarchitecture, that is, the location of the fistula and the main drainage veins were located on the dorsal or lateral side, and spinal arteries did not feed the AVF, such as most DAVF and EDAVF. Simple microsurgical treatment, where the key step is to disconnect the drainage vein close to the fistula, might be more appropriate. The posterior median approach and the far lateral approaches could be selected according to the positional relationship between the lesion and the spinal cord. For microsurgery at the CCJ region, intraoperative neurophysiological monitoring should be routinely used to help protect and detect neurophysiological function. The most common CCJ AVF was DAVF at the C-1 level; dural branch of vertebral artery (DBVA) often formed the AVF where the VA penetrated the dura. When the dentate ligament was partially removed, the drainage vein from the dura could be seen on the ventral side (figure 2). Intraoperative occlusion tests and ICG fluorescence angiography could help locate the shunt and identify abnormal vessels.[19 25 26] After disconnection of the AVF, ICG fluoroscopic angiography or intraoperative DSA was necessary to ensure complete clearance of the lesion. If intraoperative angiography was not feasible, postoperative DSA was required. The learning curve of microsurgery was steep, and familiarity with the anatomy of this region could help reduce microsurgical time and blood loss.

However, for lesions with spinal arterial feeders or those predominantly located on the ventral side, such as PAVF and some RAVF, whose architecture was more complex, often formed aneurysmal structures. For lesions located in the ventrolateral 2/3 of the spinal cord, microsurgery could be completed by rotating the dentate ligament or rotating the operating table to expose part of the ventral

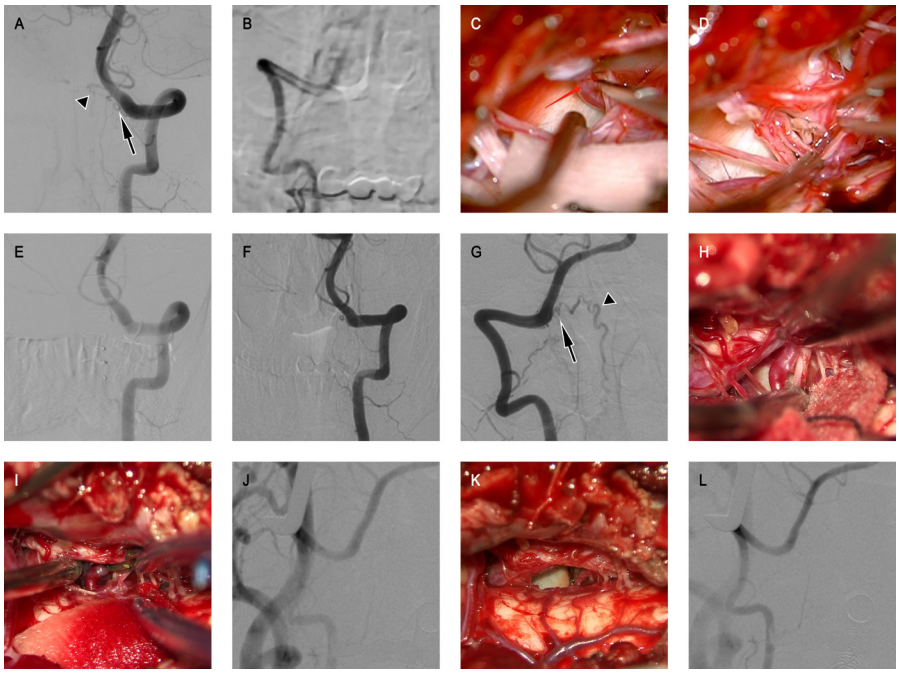

Figure 5 This male dural arteriovenous fistula (AVF) patient presented with venous hypertensive myelopathy who was treated with two times microsurgery. Preoperative angiography of left vertebral artery (VA) (A) and right VA (B). The AVF was fed by left C-1 dural branch of vertebral artery (DBVA) (black arrow in A), the feeder drains into the intradural vein (black arrowhead in A). Intraoperative image showed left AVF, the draining vein (C) and the disconnection of the AVF (D). Postoperative angiography of left VA (E) 6 days after microsurgery. Angiography of left VA (F) and right VA (G) 4 months after microsurgery. There was a newly formed AVF on the right side, which was fed by right C-1 DBVA (black arrow in G), the feeder drains into the intradural vein (black arrowhead in G). Intraoperative image showed right AVF and draining veins (H). Intraoperative image showed occlusion test to identify the draining vein (I). Intraoperative angiography after occlusion test (J). Intraoperative image and intraoperative angiography showed the disconnection of the AVF (K,L).

spinal cord; however, for lesions located in the ventral inner 1/3 of the spinal cord, which was often accompanied by aneurysmal structures fed by spinal pial arteries, it was almost impossible to clip the ventral aneurysm or disconnect the ventral drainage vein during microsurgery. Also, in the acute phase of haemorrhage, if the occlusion was not complete, this could easily lead to secondary haemorrhage. Therefore, for such CCJ AVF, we usually first performed interventional embolisation of the abnormal ventral vessels and then considered whether to perform the next microsurgery based on the postembolisation architecture (figure 3).

Placing the microcatheter in place was also challenging due to the acute angle of ASA to VA and the thin diameter of the vessel, which usually required repeated attempts. For AVFs that were not fed by ASA, interventional embolisation was generally not the first choice given the high cure rate of microsurgical treatment. The DBVAs were often very small and difficult to visualise on DSA, so interventional embolisation in such cases was very dangerous. If embolisation was performed from RA, it was important to ensure that the LSA was avoided and that the distal LSA should always be kept unobstructed during embolisation. If glue enters ASA or LSA through radiculopial artery or radiculomedullary artery, it could lead to an ischaemic event.[17 20 27] In selecting of materials for interventional embolisation of perimedullary arteries, our experience was that we preferred adhesive glue such as n-butyl cyanoacrylate (n-BCA) or Glubran 2 (GEM Srl, Viareggio, Italy). In a recent meta-analysis, Onyx was associated with significantly higher odds of initial failure or late recurrence than n-BCA (OR 3.87, 95% CI 1.73 to 8.68, I^2 0%, p<0.001) in interventional embolisation of spinal DAVF.[28] Therefore, it was crucial to correctly embolize the abnormal vessels without intraoperative complications.

In recent years, some peers have tried to treat ventral CCJ AVF with endoscope in microsurgery, which was also a novel attempt and might become a more effective treatment strategy for ventral AVF.[26 29] It has also been observed that for lesions with aneurysm structure or varix, the aneurysm structure and varix might contract spontaneously contract if only treated for AVF. Whether this phenomenon could be generalised to all patients with AVF needs to be further investigated.[20]

Outcome

In the present study, the overall complication rate was 17.2% (34/198), and the most common complication was intracranial infection. The occurrence of complications was not a factor of poor outcomes. In Takai's studies, the overall complication rate was 26% (25/97) and ischaemic complications were the most common complication. Risk analysis showed that ischaemic complications were

associated with interventional embolisation (OR 4.3, 95% CI 1.1 to 16, p=0.030) and spinal arterial feeders (OR 3.8, 95% CI 1.03 to 14, p=0.045), and patients with complications had poor outcomes (OR 5.8 95% CI 1.3 to 26, p=0.020).[20 21] In addition, this study showed that age≥56, VHM as clinical manifestation and pretreatment mRS≥3 were significantly associated with poor outcome. Therefore, these patients should be treated early and precisely. At the same time, it was important to carefully identify arterial feeders and drainage veins to avoid complications during the treatment of AVF with complex architecture, especially with spinal arterial feeders.

Previous studies reported that the retreatment rate of CCJ AVFs was 14.4% (14/97), and the retreatment rate of patients receiving interventional embolisation was higher (p<0.001).[21] In patients treated with interventional embolisation, recurrences mostly came from post-embolisation recanalisation (figure 4), while recurrence in patients who underwent microsurgery might be due to the following reasons: on the one hand, surgical trauma might increase vascular regeneration to promote new AVF formation; on the other hand, due to low blood flow and the counteracting effect of the contralateral arterial feeders, AVF fed by bilateral arterial feeders might fail to be visualised during angiography on the non-dominant arterial feeders side (figure 5). In view of the high recurrence rate of this disease, it was particularly important to review DSA regularly.

Study limitations

The present study also has several limitations. First, this was a retrospective single-centre study. The experience of our centre may not be applicable to other centres. Second, this study mainly used mRS scores for outcome ranks, which may not be sufficient to reflect subtle changes. Third, this study had a long-time span, during which the progress of treatment technology could bring changes to the treatment effect of patients, which is not reflected in this study.

CONCLUSION

SAH and VHM were the two most common clinical presentations of CCJ AVFs and the angioarchitecture of AVF, especially arterial feeders and direction of the venous drainage, resulted as important factors in the clinical presentations. Microsurgery and interventional embolisation were optional treatment strategies. The location of fistula and drainage vein was essential for choosing different treatment strategies. Generally, microsurgery was more commonly used and could be applied in most cases. Older age, VHM onset and poor pretreatment functional status predicted poor outcomes.

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Contributors YM wrote the manuscript and arranged ideas. ZS revised the manuscript and designed writing ideas. YW followed up patients and did the statistics. JW drew schematic illustrations. CH analysed imaging data. GL guided the operation and controlled the operation steps. PZ guided the operation and controlled the operation steps. TH guided the operation and controlled the operation steps. LS guided the operation and controlled the operation steps. PH guided the operation and controlled the operation steps. MY analysed imaging data and ideas supervision. HZ manuscript and ideas supervision. MY and HZ, as guarantors, were responsible for the overall content. All authors made critical revisions of the manuscript and reviewed the final version.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

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