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Pathological Spectrum of Vascular Malformations of the Central Nervous System: A Single Institution Experience of a Decade

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Abstract

Background Vascular malformations (VMs) of the central nervous system comprise a variety of lesions that could affect the arteries, veins, or capillaries.

Material and Methods We analyzed the histopathological features of all the VMs diagnosed at our centre over a decade.

Results Intracranial VM included arteriovenous malformation (AVM) (53%), cerebral cavernous malformations (CCMs) (45%), capillary telangiectasia (2%), venous angioma (0.5%), and arteriovenous fistula (AVF) (0.5%). In spinal VMs, capillary telangiectasia (40%) were the most common, followed by cavernomas (34%), AVF (16%), and AVMs and venous angiomas (5%). Clinical presentation varied from focal deficit to features of raised intracranial tension.

Conclusion Imaging and histopathology plays an important role in the diagnosis and management of VMs. Histopathological examination is essential for characterization of the VMs, which influences the prognosis.

Keywords
- vascular malformation
- histopathology
- CNS

Introduction

Vascular malformations (VMs) of the central nervous system (CNS) are a heterogeneous group of disorders which include a wide spectrum of lesions—the cerebral cavernous malformation (CCM) or cavernomas, venous angiomas, capillary telangiectasia, arteriovenous malformations (AVMs), and mixed VMs. They are increasingly recognized nowadays with the availability of advanced neuroimaging facilities. VMs account for 5 to 9% of intracranial space-occupying lesions (SOLs) and 3 to 12% of spinal SOLs.[1] There are several classification systems for VMs, the most widely accepted being the one proposed by McCormick way back in 1966.[2]

There are several reports in literature that describe individual VMs with regard to its clinical features, treatment modalities, and radiological details. However, a

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comprehensive report of the pathological spectrum of the VMs of CNS is lacking. In this study, we present the neuropathological spectrum of all the surgically resected VMs of CNS over a span of one decade from a single Institution, which is the largest study in published literature to the best of our knowledge. In this present study, we describe the clinical and histopathological features of CNS VMs with review of literature.

Materials and Methods

Ours is a secondary and tertiary referral centre in south India that has very large clientele of patients from all over the country and caters exclusively to patients with neurological, neurosurgical, and psychiatric disorders. The neuropathology department is an apex referral centre for the whole country. All VMs diagnosed in the department of neuropathology over a period of 10 years were retrieved from the archives. Demographic details, clinical features, and follow-up, wherever available, were obtained from the medical records. Resected tissues were subjected to routine processing for paraffin embedding after fixation in 10% buffered formalin. Serial sections stained with hematoxylin and eosin (H&E), Masson trichrome for evaluating collagen, and Verhoeff's modification of elastic Van Gieson were reviewed in order to categorize the cases as AVMs, CCMs, venous angiomas, arteriovenous fistulas (AVFs), and capillary telangiectasia, in accordance with the McCormick classification.

Results

The study included a total of 258 cases of surgically resected VMs, which constituted 2% of all neurosurgically resected specimens during the study period. Among 258 cases, 200 (78%) were intracranial and 58 (22%) involved the spine. Of intracranial VMs, AVMs were most common (53%), followed by CCMs (45%), capillary telangiectasia (2%), venous angioma (0.5%), and AVFs (0.5%). In spinal VMs, capillary telangiectasia (40%) were the most common, followed by cavernomas (34%) and AVF (16%), while AVM and venous angiomas were uncommon (5%). Low-flow lesions (CCM, venous angiomas and capillary telangiectasia) comprised 54% ($n = 140$), while high-flow lesions (AVMs, AVFs) comprised 46% ($n = 118$) (►**Table 1**).

The mean age of presentation was 32 years (range 2–74 years). AVFs presented in older age group, while AVMs were seen in the younger age group (►**Table 1**). Details of clinical symptoms and location are provided in ►**Table 2**.

CCMs or cavernomas were the most frequent VMs in our series, constituting 42.63% (110 cases). Of these, 81.81% (90) were intracranial and 18.18% (20) involved the spine. Mean age at presentation was 31.7 years and male:female (M:F) ratio = 1:0.7. The most common intracranial location was frontal (21 cases, 19.09%) and temporal lobe (21 cases, 19.09%). Less frequent sites of involvement were brainstem, cerebellum, ventricle, and cavernous sinus. Of the 20 cases in spinal region, there was predilection for the thoracic region (12.72%). Majority of the cases presented subacutely within 6 months of symptom onset (53 cases, 48.18%), with focal deficits (36.3%) being most common symptom. Postsurgical follow-up was available in 71% of cases, with improvement in 76% (59), persistent/new deficits in 15% (12), and recurrence in 9% (7) cases.

Histologically, CCMs were diagnosed by their characteristic conglomerate of endothelial lined, dilated vascular spaces without any intervening brain parenchyma (►**Fig. 1B-C**). The surrounding parenchyma revealed areas of hemorrhage (►**Fig. 1D**) and reactive gliosis.

Arteriovenous Malformations

AVMs constituted 41.86% (108 cases) of VMs, being most frequent in intracranial compartment (53% [105/200 cases]). Spinal involvement was extremely rare and recorded in only three patients (mean age at presentation was 29.3 years; M:F = 1.58:1). Frontal lobe involvement was most frequent (43, 39.81%). Of the 3 cases with spinal AVMs, two involved the thoracic region and one was in cauda equina. Majority presented within 6 months (55 cases, 50.92%) with symptoms of raised intracranial pressure (ICP) in 54.62% (59), followed by seizures in 16.6% (18) and focal deficits inn 9.25% (10). Follow-up was available in 64% (69), with clinical improvement in 78% (54), persistent /new deficits in 16% (11), and recurrence in 6% (4) cases.

Histologically, AVMs revealed a conglomerate of arteries, veins, and arterialized veins (►**Fig. 2C,D**). Proportion of each component varied in the nidus. Elastic Van Gieson highlighted the disruption and duplication of elastic lamina of arterialized veins (►**Fig. 2E**). Vessels showed

Table 1 Histological spectrum of VMs with frequency, age, and gender distribution

Histological type	Frequency (%)	Mean age (age range [in years])	M:F
CCM	110 (42.63%)	31.7 (2–65)	1:0.7
AVM	108 (41.86%)	29.3 (6–74)	1:0.6
Capillary telangiectasia	25 (9.68%)	41.4 (13–73)	1:1.3
AVF	10 (3.87%)	51.9 (35–66)	1:0.4
Venous angioma	5 (1.93%)	43.25 (25–60)	1:0
Total	258	32 (2–74)	

Abbreviations: AVF, arteriovenous fistula; AVM, arteriovenous malformation; CCM, cerebral cavernous malformation; F, female; M, male; VM, vascular malformation.

Table 2 Clinical features of VMs

Type	Location	Presenting symptoms	Type of presentation
CCM	Lobar = 52 (47.27%) (F = 19.09%, T = 19.09%, P = 8.18%, O = 0.9%) Brainstem = 15 (13.63%) (M = 1.81%, PO = 105, MB = 1.81%) Cerebellar = 8 (7.27%) Ventricular= 5 (4.54%) Cavernous sinus = 10 (9.09%) Spinal = 20 (18.18%) (C = 4.54%, D = 12.72%, L = 0.9%)	Focal deficits = 42(38.18%) Raised ICP = 24 (21.81%) Combined symptoms = 22 (20%) Chronic seizure = 20 (18.18%) Unknown = 2 (1.81%)	Acute = 7 (6.36%) Subacute = 53 (48.18%) Chronic = 48 (43.63%) Unknown = 2 (1.81%)
AVM	Lobar = 91 (84.25%) (F = 39.81%, T = 17.59%, P = 18.51%, O = 8.33%) Cerebellar = 13 (12.03%) Ventricular = 1 (0.92%) Spinal = 3 (D = 2, S = 1)	Raised ICP = 59 (54.62%) Combined symptoms = 21 (19.44%) Chronic seizure = 18 (16.66%) Focal deficits = 10 (9.25%)	Acute = 15(13.88%) Subacute= 55 (50.92%) Chronic = 38 (35.18%)
Capillary telangiectasia	Intracranial =2 (8%) (Sphenoid sinus = 4%, O Bone = 4%) Spinal = 23 (92%) (C = 8%, D = 76%, L = 8%)	Focal deficits = 23(92%) Combined symptoms = 2(8%)	Acute = 1(4%) Subacute= 17(68%) Chronic = 7(28%)
AVF	Lobar dural =1 (10%) (O = 1) Spinal = 9 (90%) (D = 40%, L = 40%, S = 10%)	Raised ICP = 1 (10%) Focal deficits = 9 (90%)	Subacute = 4 (40%) Chronic = 6 (60%)
Venous angioma	Dural = 1 (20%) Cavernous sinus = 1 (20%) Spinal = 3 (60%) (D = 40%, L = 20%)	Focal deficits = 5 (100%)	Acute = 1 (20%) Subacute = 2 (40%) Chronic = 2 (40%)

Abbreviations: AVF, arteriovenous fistula; AVM, arteriovenous malformation; CCM, cerebral cavernous malformation; D, dorsal; F, frontal, ICP, intracranial pressure; L, lumbar; M, medulla; MB, midbrain; O, occipital; P, parietal; PO, pons; S, sacral; T, temporal; VM, vascular malformation.

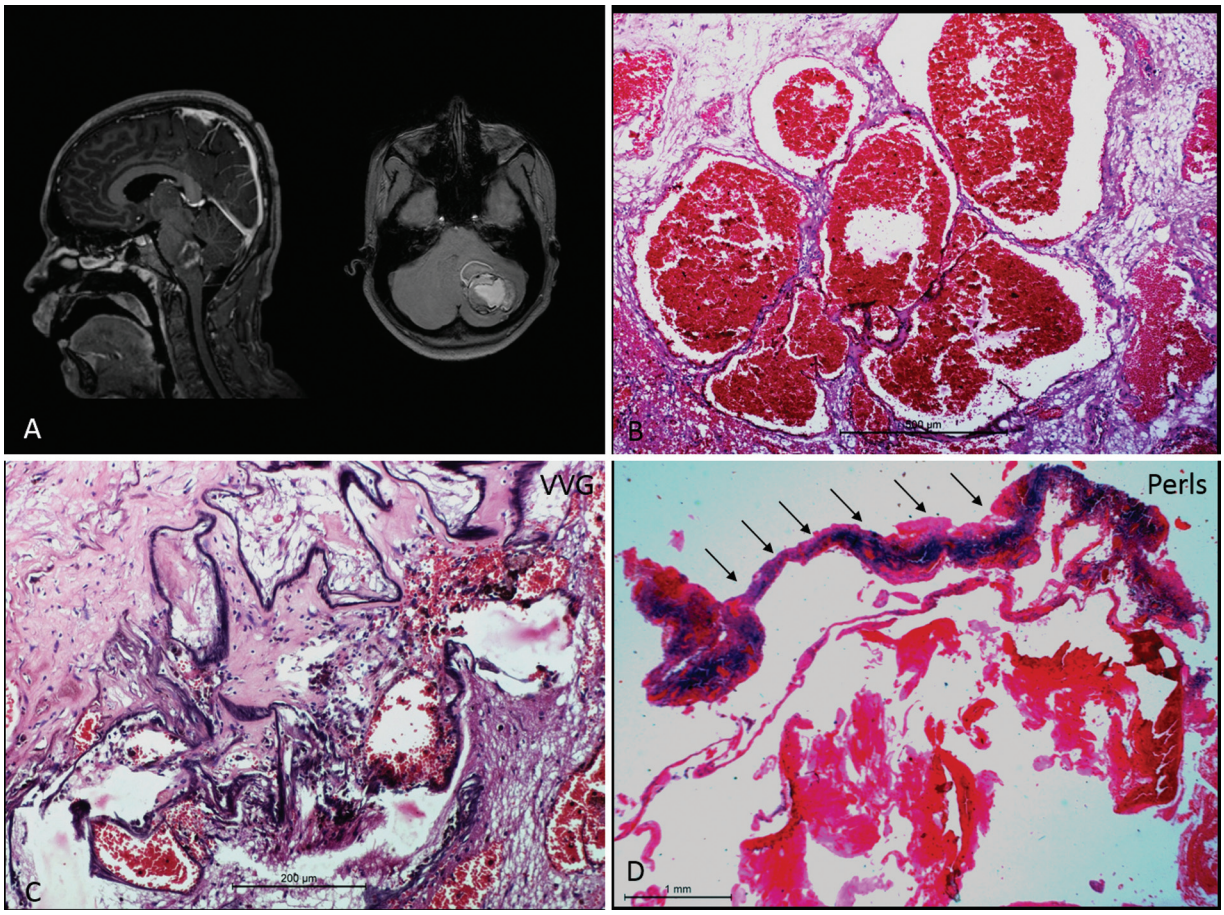

Fig. 1 Cavernoma (**A**) Postcontrast T1-weighted (T1W) and T1W MRI show heterogeneously hyperintense lesion involving the left cerebellar hemisphere and left cerebellar peduncle. Lesion is well-defined with hypointense rim and central hyperintense and isointense areas suggesting different stages of bleed. Histopathology shows a conglomerate of dilated, congested vascular channels lined by single layer of endothelium [(**B**) hematoxylin and eosin (H&E), x200) and (**C**) Verhoeff–Van Gieson (VVG), x200]. Surrounding parenchyma shows hemosiderin pigment on Perls Prussian blue stain (D) (arrows, x40).

variable degree of hyalinization and calcification (►**Fig. 2F**). The entrapped parenchyma frequently showed gliosis, hemosiderin, and inflammation. Infarction secondary to steal phenomenon was rare.

Capillary Telangiectasia

Capillary telangiectasia constituted 9.68% (25) of all VMs, involving the spinal region in majority (88.46% [23]) and infrequent in intracranial compartment (11.54% [2 cases]). They were the most frequent VMs in the spinal region, constituting 40% of all spinal VMs. Mean age was 41.4 years; M:F = 0.75:1, with predilection for the thoracic region (19, 73.07%). Focal deficits was the most frequent symptom (92%). Postsurgical follow-up was available in 71%, with improvement in 76%, persistent/new deficits in 15%, and recurrence in 9% cases.

Histologically, capillary telangiectasia was diagnosed by localized collections of dilated capillary like vessels with minimal secondary/reactive changes in the parenchyma. They lacked the dilated thin venous channels of CCMs (►**Fig. 3A**).

Arteriovenous Fistulas

AVFs constituted 3.87% (10 cases) of total VMs (►**Fig. 3C-D**). Majority involved the spine (9, 90%; [thoracic—4, lumbar—4, sacral—1]), with only a single case found in the occipital dura. Mean age was 51.9 years; M:F = 1:0.4. The single patient with occipital lesion presented with raised ICP. Postsurgical follow-up was available in 50% of cases and all showed improvement.

Venous Angioma

Venous angiomas were the least frequent (5 cases) and constituted 1.93% of total VMs, involving falx in one, spine in three (2 thoracic and 1 lumbar), and cavernous sinus in one. Mean age was 43.25 years and all were males. All presented with focal deficits.

Histologically, they showed a conglomerate of ectatic vascular spaces lined by flattened endothelium along with areas of hemorrhage (►**Fig. 3B**).

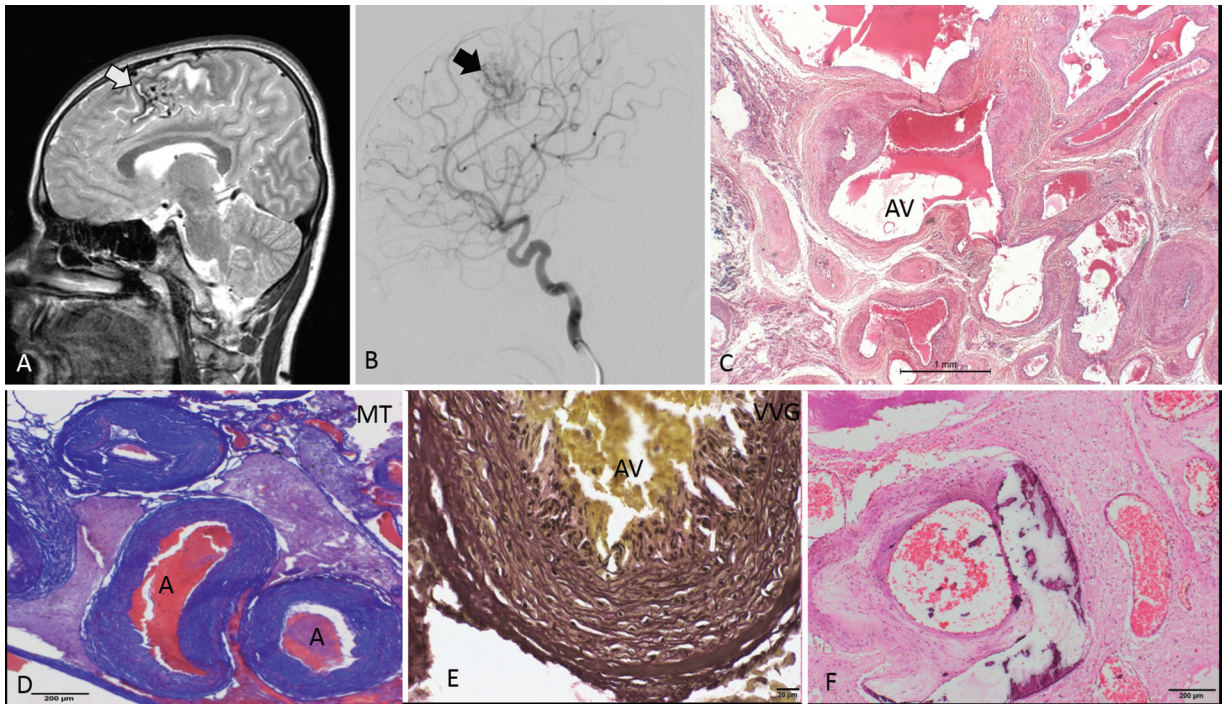

Fig. 2 Arteriovenous malformation (AVM). (**A, B**) shows sagittal T2-weighted (T2W) magnetic resonance image (MRI) and internal carotid artery angiographic image lateral view. They show abnormal flow voids in the superior frontal gyrus region with hyperintensity posteriorly and hypointense linear rim anteriorly (arrow). Angiographic image shows small compact nidus of AVM (arrow) being fed by the middle and posterior internal frontal branches of the anterior cerebral artery and being drained early by the cortical vein into the superior sagittal sinus. Histopathological examination shows a vascular malformation composed of arteries (**A**) and arterialized veins (AV) with thickened walls due to increased elastic fibers [(**C**) hematoxylin and eosin (H&E), x40; (**D**) Masson trichrome, x200; (**E**) Verhoeff–Van Gieson (VVG), x400]. Secondary changes in the form of calcification were also noted (**F**) H&E, x100).

Discussion

VMs of the CNS are important lesions that necessitate neurosurgical intervention, as they can cause serious neurological disability or even death. VMs constituted 2% of neurosurgical resected specimens during the study period at our institute. McCormick's review of 5734 autopsies revealed 4.6% incidence of cerebral VMs.[2] Jellinger et al reported a higher incidence, with VMs representing 5 to 9% of intracranial SOL and 3 to 12% of spinal SOLs.[1] Inclusion of only symptomatic surgically resected VMs in our series explains the lower incidence in our series.

CNS vascular system develops as a result of controlled interplay between mesodermal vascular cells and derivatives of neuroectoderm. Any disturbance in this regulated development causes malformations, which may involve arteries, capillaries, or the venous channels.[3] Majority of these lesions are congenital in origin and hence resemble early embryonic vasculature. In 1966, McCormick classified CNS VMs into four subtypes: AVMs, cavernous malformations, capillary telangiectasia, and venous malformations. Later, it was recognized that a proportion of these lesions show a combination of the subtypes with advancements in imaging techniques. VMs can be sporadic or familial and can also be associated with syndromes such as Osler–Weber–Rendu or hereditary hemorrhagic telangiectasia. Genetic alterations are being increasingly recognized in familial and syndromic associations of VM, which resulted in emergence of more detailed classification.[4] The International Society for the Study of Vascular Anomalies (ISSVA) classification recently adopted a classification scheme that separates "vascular tumours" secondary to active proliferation from "vascular malformations," due to developmental defects in vascular morphogenesis which differ in clinical profile, diagnostic, and therapeutic strategies.[5]

Large series documenting the complete histological spectrum of VMs with clinicopathological details are scarce in literature. Most studies describe individual types of VMs in the context of seizure causation, neuroimaging, and treatment modalities. In this study, we documented the clinicopathological spectrum of surgically resected VMs over the last 10 years at our institute, a referral center that caters exclusively to patients with neurological and psychiatric disorders. We found only one other study that documented spectrum of 50 cases of VMs.[6]

Most common VMs are AVMs and CCMs, with detection rates of approximately 1.1 and 0.6 per 100,000 adults per year. In our series, CCM were the most common VMs overall, AVMs being the most frequent amongst intracranial VMs and hemangiomas and AVF being most common in spine. This is similar to a population-based study by Mac Donald et al, who reported 54% of intracranial VMs were AVMs.[7] In a study by Karri et al in south India, CCMs were found to be more common than the AVMs, accounting for 72% (36/50) of all VMs.[6]

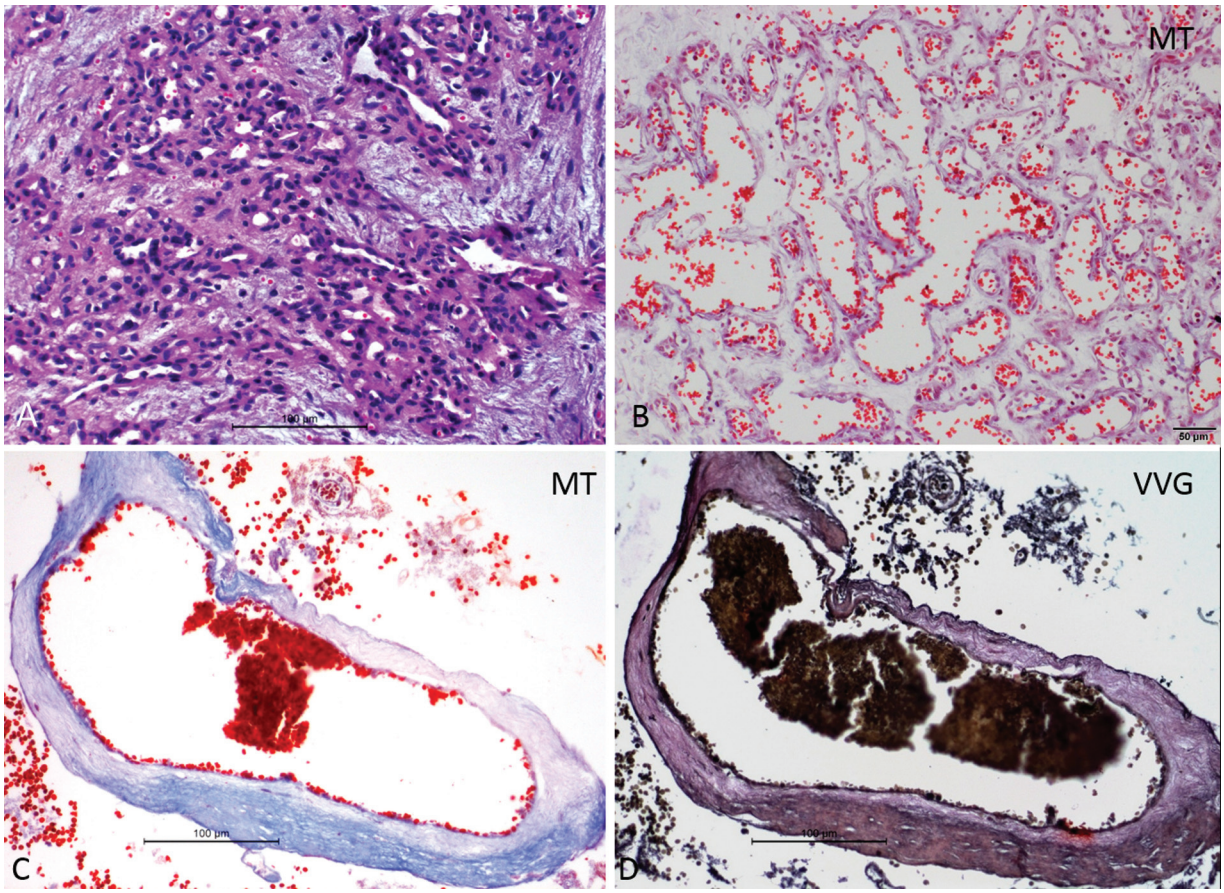

Fig. 3 Capillary hemangioma composed of closely packed capillary sized vascular channels [(**A**) hematoxylin and eosin (H&E), x100], cavernous malformation with back-to-back arranged dilated thin walled vessels [(**B**) Masson trichrome, x100]. Arterialized vein of an arteriovenous fistula [(**C**) Masson trichrome, x200 and (**D**) Verhoeff–Van Gieson (VVG), x200]..

AVMs are usually sporadic and rarely familial.[8] They are high-flow shunts between arterial and venous channels without an intervening capillary network. When congenital, they result from retention of embryonic vasculature, with remodeling and added angiogenesis, or they can be secondary to a postnatal event, resulting in angiogenesis. Angiogenic factors, including VEGF and endothelin1, have been associated with AVMs.

AVMs constituted 41.86% (108 cases) of VMs and 51.7% of intracranial VMs in our series. AVMs were more frequent in intracranial compartment 97.22% (105/108 cases), with only 3 cases involving the spinal region. As much as 65% of intracranial AVMs are hemispheric, 15% involve deep midline structures, and 20% are known to occur in posterior fossa.[9] Frontal lobe was the most common site involved in our series (39.81%) and 12.03% in posterior fossa. Peerless et al also documented posterior fossa involvement in 10% of AVMs.[10] AVMs tend to have male preponderance and younger age at presentation, as noted in our study as well (Perret et al and Hofmeister et al).[9,11] Raised ICP secondary to hemorrhage, followed by generalized and focal seizures, is common clinical presentation[12] noted across various studies, which is in concordance with our study.

CCMs were the second most common intracranial VMs in our study (44.33%). They are hamartomas which can either be sporadic or inherited. Familial forms have a higher incidence (30%) with an autosomal dominant form of inheritance.[8] They occur in about 0.4 to 0.8% of the population, and account for 10 to 15% of all CNS vascular lesions, making them the second most common CNS VM. They have predilection for the cerebral hemispheres, pons, as well as the spinal region.[12] Spinal cavernomas accounted for 18.18% in our series. Reitz et al reported that intramedullary cavernomas account for 5 to 12% of all vascular pathologies.[13] Similar to AVMs, cavernomas present in patients younger than 50 years and have a male predilection. Patients may present with seizure, focal neurologic deficits, or acute intracranial hemorrhage, depending on the site of involvement. Many small, cavernous malformations that present with large intracerebral hematomas may be excised at the time of hematoma resection. O Del Curling et al have noted seizures in 42% and focal deficits in 25%.[14] In our study, the focal deficits were seen in 36.3%, followed by raised ICP in 20.9% and chronic seizures in 18% of the cases.

Capillary telangiectasia were the most frequent VMs in the spinal region, constituting 40% of spinal VMs. They are most often congenital and maybe found in association with other VMs. There is invariably an incidental finding involving the pons. Most of the other studies have described the mean age of presentation as 5th decade with no obvious sex predilection.[15,16] Majority of our cases presented with focal deficits due to intratumoral bleed and cord

compression. Higher incidence of subacute and chronic presentation in our series are also explained by the slowly progressive spinal cord damage because of repeated bleeds.

Less commonly encountered lesions are AVFs and venous angiomas. AVFs constituted 3.87% of VMs in our study in the spinal region, accounting for 15.5% of cases, whereas Maimon et al noted that AVFs constituted 60 to 80% of spinal VMs.[17] The discordance is attributed to inclusion of only surgically resected cases in our series. AVFs are distinguished from AVMs by the presence of a direct, high-flow fistula between artery and vein. There is no intervening nidus. They are postulated to develop secondary to venous obstruction either in the fetal phase or adulthood. Venous angiomas are usually asymptomatic. Onset of AVF peaks in the fifth and sixth decades, similar to our study. Clinical manifestations result from pressure effects of the lesion.

Venous angiomas are referred to as developmental venous anomalies, which arise from the maldevelopment of fetal cortical veins. They are usually asymptomatic. We had four cases of venous angiomas in our series wherein one involved the falx, whose excision resulted in venous infarct. The other three cases involved the spine. All the cases were males between third to fourth decade and presented with focal deficits due to pressure effects of the lesion.

Treatment strategies for VMs include surgery, radiosurgery, embolization, or conservative management, depending on the site and size of VM. Majority of these lesions respond to treatment with few complications such as haemorrhage or rarely recurrence. In our series, more than 75% of the patients responded well to treatment.

Vascular malformations of CNS are a diverse group of lesions, the clinical effects of which depend on its location, type (high flow vs. low flow) and associated hemorrhage. The reported spectrum of VMs documented in this study will not reflect population incidence, but the hospital-based incidence of malformations that were subjected to surgical excision. Several VMs maybe asymptomatic or incidental, and others may be treated with noninvasive means with major advances in interventional radiology. Imaging and histopathology is critical for diagnosis, categorization, and management, which have an impact on patient prognosis.

Note

The study is a retrospective review of histopathological and clinical data from case records. Consent to use the tissue for research purpose was taken at the time of surgery.

Conflict of Interest

None declared.

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