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Central Nervous System Vascular Malformations

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1. Introduction

A detailed understanding of vascular anatomy and embryology is essential to facilitate appropriate decision-making by clinicians responsible for treating vascular malformations of the central nervous system. The development of the cerebral vasculature has been extensively described in the original works of Streeter [1, 2] and Padgett [3-5], and summarized by Davidson and Morgan [6].

1.1 Development of the cerebral arterial system

With the growth of the developing embryonic brain, increasing requirements for oxygen and metabolic substrates demand a more comprehensive and complex vascular system. Covering the entire neuraxis is a primitive network of mesenchymal cells known as the meninx primitiva. The meninx follows the folds that appear during development of the brain, filling the interhemispheric fissure that forms between the two lateral telencephalic bulges to ultimately become the falx cerebri. At this early stage (embryo < 4 mm length), there is no differentiation into arteries and veins; the irregular network of endothelial vascular channels constitutes a primitive germinal bed of endothelium rather than a true circulatory system. The meninx primitiva differentiates into three discreet layers, which will ultimately become the dura mater, the arachnoid, and the pia mater [7]. Ultimately, angioblastic cells from the meninx become applied to the superficial surface of the developing brain, then penetrate the surface and extend perpendicularly to the pial surface between the glial elements, forming an extensive capillary-like network of endothelial cells (endothelial "buds") [2, 7-9].

Vascular buds ultimately coalesce into larger vascular channels, with afferent channels forming arteries and efferent channels forming veins. On the pial surface of the brain, arterial vessels rise above those that become venous, and where these vessel cross, the artery crosses the vein at approximately right angles. Islands of endothelial cells proliferating within the outer layer of the meninx will eventually coalesce to form the dural venous sinuses; those within the middle layer will develop into the major veins that link the cortex to the dural venous sinuses, and the vessels that ultimately supply and drain the brain parenchyma develop from the inner layer [2].

The primitive internal carotid artery (ICA) develops mainly from the third aortic arch (although minor contributions are made from the first and second arches as well). During the early stages of brain development, the ICA supplies most of the blood to the entire brain through several named branches including the trigeminal, hypoglossal, otic, and the proatlantal intersegmental arteries. These primitive branches are usually transient, although rarely they persist in adults.

Next, two parallel collections of primitive arterial arcades appear along the lateral aspect of the rhombencephalon. These longitudinal neural arteries are supplied from the ICA via the trigeminal arteries, and from what will become the posterior circulation via the developing cervical intersegmental arteries. Ultimately, most of these vascular communications recede, with the fused portion of the longitudinal neural arteries forming the midline basilar artery, and the posterior communicating artery replacing the tentorial artery as the source of collateral supply between the anterior and posterior circulation.

Later, the cervical intersegmental arteries develop into the paired vertebral arteries, and the anterior cerebral artery, anterior choroidal artery and middle cerebral artery arise from the ICA. An arterial plexus develops deep within the anterior interhemispheric fissure, which will later become the anterior communicating artery. Through a series of arterial anastomoses and regressions, the primitive dorsal and ventral ophthalmic arteries evolve into the adult form of the ophthalmic artery. Further evolution of the middle cerebral artery occurs, with hemispheric branches and choroidal arteries developing further, and the posterior cerebral artery arises from the ICA.

Finally, the major components of the arterial Circle of Willis near completion, with the posterior cerebral artery taking up the majority of its supply from the posterior circulation, leaving the posterior communicating artery as an embryological remnant in the majority of cases. The development of the cerebellar arteries occurs later, corresponding to the delayed development of the cerebellum compared to the cerebrum.

1.2 Development of the cerebral venous system

At about the 4 mm stage of embryonic development, a primordial venous channel develops within the meninx primitiva, called the vena capitis medialis. This carries no flow, and merely represents proliferative endothelial cells. The vena capitis medialis quickly disappears, and in its place the vena capitis lateralis, or primitive head sinus, forms. The primitive head sinus develops into three separate dural venous plexuses – anterior (telencephalic, diencephalic, and mesencephalic), middle (metencephalic), and posterior (myelencephalic). The primitive maxillary vein joins the primitive head sinus as its only direct tributary, which drains the optic vesicle.

In subsequent stages, the anterior, middle and posterior plexuses of the primitive head sinus unite to become the adult transverse and sigmoid sinuses [7]. The inferior portion of the primitive head sinus later migrates laterally to become the internal jugular vein, whilst the cranial portion of the sinus ultimately becomes the cavernous sinus.

As the telencephalii develop and expand, expansion of the anterior dural venous plexus occurs, and it is the medial aspects of these expansions that fuse to form the primitive marginal sinus, which fuses with its contralateral counterpart to form the early superior

sagittal sinus. This is the dominant venous structure anteriorly, and with further development it progressively incorporates more posterior portions of the dural venous sinuses.

With deepening of the interhemispheric fissure, and lateral evagination of the telencephalic-diencephalic sulcus, the choroidal fissures form. The meninx primitiva, primitive choroid, and arterial supply are drawn into the fissure, which drains via the median prosencephalic vein [7]. With the development of the basal ganglia, primitive internal cerebral veins form and fuse in the midline to form the vein of Galen and straight sinus, replacing the median prosencephalic vein as the main venous drainage of the choroid plexus. The caudal remnant of the median prosencephalic vein becomes part of the vein of Galen complex. Persistence of the median prosencephalic vein is a common finding in vein of Galen malformations. The presence of a persistent falcine sinus (which normally regresses as the straight sinus develops) is also indicative of the arrested venous development that commonly occurs in the setting of a vein of Galen malformation [10].

As the developing cerebral and cerebellar hemispheres expand, the dorsal meninges at the junction of the prosencephalon and mesencephalon remain relatively fixed, forming the tentorial edge. The plexus of veins within the leaves of the tentorium and the tentorial sinus (located medially within the tentorium) persist until after birth [8]. The expanding cerebral hemispheres exert more of an influence on the orientation of the tentorium than the cerebellum, and the tentorium changes from its initial vertical orientation to a more horizontal alignment, causing the transverse sinus to alter its vertical alignment to a more horizontal direction.

Development of emissary veins occurs during the latter stages of venous development. Elongation of the primary pial vein during development of the diencephalon and telencephalon produces the basal vein of Rosenthal, which secondarily becomes connected to the internal cerebral vein [7]. Elongation of the numerous subarachnoid veins that bridge from pia to dura during enlargement of the cerebral hemispheres results in the superficial anastomotic veins, including the vein of Trollard and the vein of Labbé. The middle cerebral vein assumes its adult form only after closure of the Sylvian fissure, and remains separate from the cavernous sinus until after birth [8]. The presence of arteriovenous malformations (AVMs) with venous drainage into the Sylvian veins and cavernous sinus suggests that these malformations develop post-natally.

Although the arterial system is well formed by the end of the embryonic period, the venous system continues to evolve until late in fetal development, with some important changes to the developing venous system occurring after birth.

2. Arteriovenous malformations

2.1 Theories of pathogenesis

AVMs have traditionally been considered congenital lesions, occurring as a result of disordered development of the primordial vasculature in a process described by Yaşargil as a 'proliferative capillaropathy' [11]. This hypothesis has become enshrined as neurosurgical doctrine, even in the absence of any strong evidence to support the theory.

As early as 1984, doubts had arisen regarding the congenital nature of AVMs. Warkany and Lemire recognized that AVMs *"are generally considered congenital, although patients usually are adults 20 to 60 years of age and few have signs or symptoms that go back to early life"*. They acknowledge that AVMs *"are puzzling to teratologists because they occur sporadically and are unassociated with congenital malformations outside the central nervous system"*, and point out *"the unsatisfactory state of our understanding of these malformations … and recommend them to teratologists for further study"* [12]. In his 1996 paper on the embryological basis of AVMs, Mullan noted that the *"theories of origin are not susceptible to experimental proof and should be accepted or rejected on the basis of the available evidence"* [8].

Conflicting evidence exists regarding the pathophysiology of brain AVMs, with reports of clinical cases supportive of both post-natal development and an embryologic origin [6]. A study examining the difference between birth-to-diagnosis and diagnosis-to-hemorrhage timelines in over 1500 cases suggested that a biological change occurs around 10 years from birth that influences hemorrhage rates in patients with AVMs. The authors concluded that the AVM either was not present before age 10 years, or was present but was biologically inactive prior to this stage [13].

As further research is undertaken exploring the molecular biology of AVMs, evidence is accumulating in support of the alternative hypothesis – that AVMs are an acquired abnormality, developing in the postnatal period. Although an initiating event has yet to be defined, possible candidates include trauma, tissue hypoxia, venous hypertension, infection, inflammation, irradiation, or compression [14, 15]. The primary vascular defect may be the development of a simple arteriovenous fistula [16], with altered hemodynamic stresses occurring in the affected vessels. Further pro-angiogenic vascular remodeling and secondary vascular changes would occur secondary to the hemodynamic stress, producing the characteristic AVM seen in clinical practice [17].

2.2 Genetics

Relatively few cases of familial occurrence of AVM have been reported [18], and genome-wide linkage studies in twins have failed to identify a genetic locus for inherited AVM [19]. Although familial cases can occur, AVMs typically occur in a sporadic fashion [20].

One exception to this rule is the development of multiple AVMs in patients with hereditary hemorrhagic telangiectasia (HHT, or Rendu-Osler-Weber syndrome). HHT is an autosomal dominant disorder producing vascular malformations in multiple organs [21]. Small mucocutaneous telangiectasias typically occur in the oral cavity, nose, conjunctivae, and on the fingertips; AVMs occur in the lung (50% of HHT patients), liver (30%), brain (10%), and spine (1%) [22]. HHT patients represent a very small subset of patients with AVMs (approximately 2% of all AVM patients) [23, 24].

HHT usually results from mutations in the Endoglin (HHT1) gene, or ACVRL1 (HHT2) gene; other less common subtypes include HHT in association with juvenile polyposis (JPHT), HHT3, and HHT4. All of the genes responsible for HHT are involved in the transforming growth factor (TGR-β) superfamily signaling pathway, and mutations result in the development of abnormal vascular structures [22].

The prevalence of AVMs in the population is approximately 0.01% [25]. The estimated prevalence of AVMs in the population of patients with HHT is approximately 5-10% [26],

although this may be an under-representation because of the controversy surrounding screening of asymptomatic patients for brain AVMs [22]. In one study where screening was performed in 268 of 1291 HHT patients, 15% of HHT1 patients and 1% of HHT2 patients harbored AVMs [21].

There is an increased risk of multiple AVMs in HHT patients [27]. AVMs in HHT patients do not follow the typical pattern of sporadic AVMs; they can grow or regress, and can recur after angiographically confirmed complete resection [28].

Other developmental syndromes associated with brain AVMs include Wyburn-Mason syndrome and Sturge-Weber syndrome [29-31]. The pathogenesis of these developmental abnormalities is poorly understood, and provides little insight into the molecular biology of sporadic AVMs.

Several studies have examined gene expression in AVMs using gene microarray techniques, with hundreds to thousands of genes of interest reported. In one study, where over 1700 differentially expressed genes were identified, the majority belonged to angiogenesis, vascular matrix, or apoptosis pathways [32]. Significantly upregulated genes include those coding for Ang-2, VEGF-A, the VEGF receptor (Flt1), Integrin αv, Endoglin, MMP-9, and Ephrin-A1; significantly downregulated genes include Krit1, Ang-1, Tie, Tek, Laminin α3, Smoothelin, and Connexin 37 [32-35]. Conflicting gene microarray results have been obtained for CD31 (PECAM-1), with one study demonstrating upregulation, and another demonstrating downregulation [32, 34].

Gene single nucleotide polymorphisms (SNPs) have also been studied in groups of patients with AVMs, with a view to identifying potential genes that may be of prognostic and pathophysiological significance. Polymorphisms in the IL-6, IL-1β, TNF-α, and apolipoprotein-E (ApoE) genes have been associated with increased risk of hemorrhage [36-39], and SNPs in ALK-1 are associated with a susceptibility for AVM formation [15].

2.3 Clinical features

Arteriovenous malformations most commonly present in young patients, with a mean age at diagnosis around 35 years. There does not appear to be a gender predilection. They most commonly present with hemorrhage; many population-based studies and large natural history studies demonstrate that approximately 50% of patients present with AVM rupture [40-51]. The next most common presenting feature is seizure, with 24-36% of patients presenting with generalized or partial seizures. Other reasons for presentation include focal neurologic deficit [52], headache [53-55], or as incidental imaging findings in asymptomatic patients [56, 57].

2.4 Diagnosis, including early detection

Noninvasive imaging modalities including CT, CT angiography, MRI, and MR angiography are extremely valuable in the diagnosis and characterization of brain AVM. Determination of proximity to eloquent structures and accurate measurement of nidal dimensions is important in determining surgical risk. In selected cases, functional MRI [58] and diffusion tensor imaging-based tractography [59] may be useful for providing additional information

about the relationship of an AVM to critical neurological structures. Non-enhanced CT and gradient-echo or susceptibility-weighted MRI sequences are particularly useful in demonstrating previous hemorrhage. However, digital subtraction angiograpy remains the gold standard for demonstrating AVM angioarchitecture, and is essential for planning appropriate management strategies [60].

2.5 Treatment

Several options are available for the management of patients with AVMs: microsurgical resection, stereotactic radiosurgery, endovascular treatment, multi-modality treatment, or observation. The preferred management option in each case depends on many factors, including AVM specific factors (such as size, location, arterial and venous anatomy, and mode of presentation), institutional factors (experience of cerebrovascular surgical team, access to stereotactic radiosurgery, availability of endovascular treatment options,), and patient factors (general medical condition, co-morbidities, age, patient preference).

In determining the most appropriate management for an individual patient, the surgeon must balance the risk of intervention with the risk of the natural history and recommend the safest, most efficacious option. Sometimes, the safest option is to do nothing [61]. Ultimately, the risks of management must be acceptable to the patient.

2.6 Prognosis

Without treatment, the overall risk of AVM hemorrhage has been estimated to be 2 to 4.6% per year [40-46]. Previous hemorrhage is a significant risk factor for further hemorrhage; the risk may be as high as 18% in the first year after hemorrhagic presentation [62], returning to baseline within 5 years [63]. Large AVM size, deep and infratentorial location, deep venous drainage, and the presence of associated aneurysms have also been implicated as factors associated with a higher risk of rupture.

Early studies, relying on retrospective audits of hospital charts and taken from the era before modern brain imaging and improvements in intensive care management, reported neurological morbidity and mortality as high as 52-81% following AVM hemorrhage [41, 42, 64]. More recent studies have indicated that the morbidity from AVM hemorrhage is not quite as bad as these figures suggest, with 30-47% of patients suffering a neurologic deficit resulting in a modified Rankin Scale score (mRS) > 1 [44, 65, 66]. Long-term population studies have demonstrated that untreated AVMs are associated with a significant risk of long-term excess mortality that is dramatically reduced but not completely normalized following total excision or occlusion of the AVM [67].

Numerous authors have reported the results of surgical resection. It is generally accepted that the risk of surgery is low (<10%) in Spetzler-Martin (SM) grade 1 and 2 lesions [68-71]. Spetzler-Martin grade 3 AVMs are a heterogenous group, and complication rates depend largely on the morphology of these lesions, with some having a risk profile similar to that of small (SM grade 1 & 2) AVMs, and some having a risk profile similar to that of large (SM grade 4 & 5) AVMs [72-74].

Very few series report the results of surgery for large or giant AVMs. There are many groups who advocate against surgery for SM grade 4 & 5 AVMs because of the perceived

high risk of surgery [75]. In those series where surgery was undertaken, even in carefully selected patients, complications occurred in up to 30% [76-81].

Ultimately, each of these sets of published results needs to be taken in context, as the results from different neurosurgical centers will differ as a result of referral patterns, treatment selection biases, and experience of the clinicians. Davidson and Morgan reported the risk of surgery in 640 patient with brain AVM, including an analysis of cases excluded from surgery because of the perceived surgical risk; in this series, the observed risk of adverse outcome related to surgery in SM Grade 1 & 2 patients was 1%, the risk in Grade 3 patients was 14%, and the risk in Grade 4 & 5 patients was 34% [82].

The primary goal of AVM treatment with stereotactic radiosurgery is to obliterate the nidus without the need for operative surgical intervention, removing the risk of future hemorrhage. The efficacy of AVM radiosurgery is much lower than with surgery (obliteration rates range from 36% to 92%, depending on the size of the lesion treated) [83, 84]. Unlike surgery, obliteration is delayed by up to 3 years, and during this time the AVM is still at risk of rupture [85].

There are many reports in the literature relating to the risks of stereotactic radiosurgery, including the risk of rupture during the 'latent interval' between treatment and AVM occlusion. More recent series report hemorrhage after radiosurgery in 3% to 9% of patients [86, 87], radiological imaging changes in up to 46% to 66% (severe in 19%) [84, 88], transient neurological complications in 5% to 17% [89, 90], and permanent neurological complications in 1% to 13% [89, 91].

Complete occlusion of an AVM is rarely achieved with endovascular treatment alone, with most published angiographic cure rates ranging from 16-28% [92-97]. Many of the angiographic cures are in small AVMs, with very few complete occlusions in SM grade 3 AVMs or larger. Even in the most experienced hands, complete occlusion was reported in 51% of patients; however, only 12.5% of patient with SM Grade 3-5 AVMs experienced angiographic cure after Onyx embolization [98]. Combined morbidity and mortality rates in these series range from 5-12%, with more aggressive attempts at complete occlusion generally resulting in higher complication rates [93].

Although multi-modality treatment (incorporating combinations of surgery, embolization, and radiosurgery) appears to be an attractive option for treating these large lesions, cure rates are only in the order of 36% [76], and the cumulative effects of treatment-related morbidity may be much higher than single- or dual-modality management.

2.7 Screening of relatives

There is currently no evidence to support the use of diagnostic imaging to screen for the presence of brain AVMs in asymptomatic patients. However, considerable controversy surrounds the role of screening in HHT patients. Some authors argue that the low risk of hemorrhage combined with the significant risk of treatment does not support the use of screening [22]; others have demonstrated a higher risk of hemorrhage in HHT patients with asymptomatic AVMs, and argue in favor of screening [99]. In these patients, the use of non-invasive imaging (such as MR angiography or contrast-enhanced CT angiography) may be considered.

3. Dural arteriovenous malformations

3.1 Theories of pathogenesis

The earliest discussions of the pathogenesis of dural arteriovenous malformations (DAVMs) focussed on a possible congenital origin [100-103]. Reinforcing this belief is the observation that 3% of DAVMs present before the age of 1 year [104]. The occurrence of DAVMs in the neonatal and pediatric population suggests that congenital factors are at play in at least some of these lesions. Dural sinus malformations almost certainly represent disorders of embryonic venous development [105]; it is unclear whether infantile type DAVMs represent a similar embryological malfunction or reflect a response to intrauterine thrombosis. Adult-type fistulous DAVMs are extremely rare in the pediatric population, representing 0.8% of all pediatric vascular malformations [105]. It is now thought that most of these lesions are acquired in adulthood, and that that congenital DAVMs are exceptionally rare.

Possible precipitating factors such as trauma, tumour, cerebral thrombophlebitis, neurological surgery, or ENT infection, can be demonstrated in 15-32% of cases [106-109]. By including patients with generalised hypercoagulable states (such as peripheral DVT, pregnancy, and use of oral contraceptive pill), a large meta-analysis reported that 66% of DAVMs had some possible predisposing factor [110]. In the remainder, however, no demonstrable precipitant can be identified, and the DAVM is considered to be idiopathic.

Two hypotheses have been proposed in an attempt to explain the development of spontaneous or idiopathic DAVMs. In the first, neovascularization of an organising thrombus within a dural venous sinus is described as the primary event leading to the development of a DAVM [111]. The second theory suggests that some unspecified event (which may be a factor other than venous sinus thrombosis) results in opening of physiological arteriovenous shunts normally located within the dura mater [112, 113].

3.2 Genetics

In contrast to parenchymal AVMs of the brain, which may be congenital lesions, DAVMs are now thought to be acquired. DAVMs have been reported to occur in patients with various systemic conditions, particularly syndromes characterised by connective tissue disorders. Potential associations include: atypical Sturge-Weber related syndrome [114], blue rubber-bleb nevus syndrome [115], congenital toxoplasmosis [116], Ehlers-Danlos syndrome [117-119], fibromuscular dysplasia [117, 120, 121], hereditary hemorrhagic telangiectasia [122, 123], Marfan's syndrome [124], osteogenesis imperfecta [117], polyarteritis nodosa [125], pseudoxanthoma elasticum [126], Rendu-Osler-Weber syndrome [127], syndactyly [128], and von Recklinghausen's disease [129].

These reports are generally isolated to single cases, and whilst an association may be proposed on the basis of sound physiological principles, there is little convincing evidence of a causal relationship.

3.3 Clinical features

The clinical features of DAVMs are almost exclusively related to the pattern of venous drainage. Very few clinical manifestations have been related to arterial phenomena and all of these clinical scenarios can be equally well explained by venous hypertension and

congestion causing focal impaired perfusion of neural structures [111, 130]. No angiographic evidence for arterial 'steal' in DAVMs has ever been provided. Orbital venous congestion and hypoxic retinopathy have been proposed as suitable explanations for the common ophthalmological symptoms occasionally attributed to arterial insufficiency [131]. Elevated ocular venous pressures may result in oedema and inflammation in surrounding extra-ocular muscles, causing diplopia unrelated to cranial nerve compression [108].

In most DAVM series, pulsatile tinnitus is the most common complaint, occurring in up to two thirds of patients [132-134]. A bruit is detectable in a variable proportion of patients with subjective tinnitus, with reports ranging from 40% [135] to 96% [136].

In the presence of a DAVM, venous hypertension may occur through one of two mechanisms: increased blood flow through a draining vein, caused directly by arteriovenous shunting; or restricted venous outflow distal to the DAVM (including sinus occlusion) as a result of increased blood flow, elevated pressures, and turbulence in the draining vein [137, 138]. Venous congestion is capable of producing neurological deficits [139], and when this occurs locally, focal neurological deficits occur.

Orbital venous hypertension may result in the 'red-eyed shunt syndrome' [140] or 'dural shunt syndrome' [141]. In the presence of a direct, high flow carotico-cavernous fistula (CCF) the clinical features can occur dramatically; however, with an indirect, low-flow DAVM the patient may be asymptomatic, or gradually develop symptoms that are generally less severe than with a direct CCF [126, 140, 141].

Headache is one of the most common complaints leading to a neurologic assessment [142]; however, patients often present with incidental headache unrelated to their pathology. The headache attributed to DAVM is likely to occur in conjunction with signs of intracranial hypertension due to a decrease in venous outflow or sinus thrombosis [143]. Clinicians must rely on the clinical features of headache to differentiate a clinically significant secondary headache from an unrelated benign headache. These clinical features include: sudden onset of headache; worsening pattern of headache; headache with systemic illness or focal neurological signs and symptoms, including papilledema; headache triggered by cough, exertion, or Valsalva manouver; and headache during pregnancy or post-partum [142].

As opposed to parenchymal AVMs, DAVMs consist of a nidus that is supported by a strong collagenous and fibrous stroma (the dura mater), and as such the nidus of a DAVM is rarely the source of hemorrhage [144]. Accordingly, the presence of retrograde parenchymal venous drainage has been shown to be the primary factor responsible for intracranial hemorrhage in DAVMs. It is the parenchymal veins that traverse the space between the dura and the adjacent brain that are generally the source of intracranial hemorrhage in DAVMs [145]. When these veins fail under hemodynamic stress, intracerebral, subarachnoid, or subdural hemorrhage may occur. Of these anatomical locations, intraparenchymal hemorrhage occurs most commonly [146].

Increased venous pressure at the torcular region can cause headaches, papilledema, and infantile hydrocephalus as a result of global venous hypertension [104]. At the more severe end of the spectrum, global venous hypertension with gross impairment of cerebral venous drainage may result in a more severe, progressive, generalized neurological deficit [147]. Patients may present with an extrapyramidal movement disorder, similar to Parkinson's

disease [148, 149]. In extreme cases, patients may present with progressive global cognitive decline, which is often mistakenly diagnosed as Alzheimer's dementia. The dementia occurring as a result of DAVMs presents as a severe, rapidly progressive cognitive decline that resolves following obliteration of the DAVM in most cases.

3.4 Diagnosis

Angiography is the most important diagnostic test in the evaluation of a patient suspected of having a DAVM. Complete 6-vessel cerebral digital subtraction angiography, including assessment of bilateral internal carotid, external carotid, and vertebral arteries is required to confirm the diagnosis, and to adequately define the dural origin of the nidus, the arterial supply, and the pattern of venous drainage. Other imaging modalities may be useful when used in conjunction with angiography.

Standard axial CT images are useful in patients with DAVMs, and are able to complement the angiographic findings by adding information on the following: cerebral abnormalities (including intracranial hemorrhage, cerebral edema, hydrocephalus, infarction, and contrast enhancement of dilated intradural venous structures), osseous abnormalities, and abnormal dural enhancement.

MR imaging plays an important complementary role in the evaluation of DAVMs, particularly in the evaluation of venous congestion, local and regional perfusion, and the assessment of venous sinus thrombosis [150]. It may also permit non-invasive follow-up of treated lesions.

3.5 Treatment

Various management options are available for the management of cranial DAVMs: compression therapy, surgical intervention, endovascular treatment, radiation therapy, or observation. The preferred management option in each case depends on many factors, including DAVM specific factors (such as the location of the DAVM, pattern of venous drainage, number of arterial feeders), institutional factors, and patient specific factors. The natural history of DAVMs with retrograde parenchymal venous drainage suggests that treatment should be considered unless unusual circumstances make the risks of intervention prohibitive. A more conservative approach may be considered in patients with a benign DAVM. The reasons for considering treatment in these patients include progressive neurological deficit (including progressive orbital venous hypertension), or disabling tinnitus.

In a meta-analysis of treatment options, surgery (either alone or in association with pre-operative embolization) was the most effective management option for DAVMs located in the transverse or sigmoid sinus, tentorial incisura, and anterior cranial fossa (ACF) [110]. The small number of cases of superior sagittal sinus (SSS) DAVMs precluded a meaningful statistical analysis; however, the authors also recommended surgical treatment in this group.

With the development of better techniques and materials, the role for endovascular treatments in the management of DAVMs continues to evolve. Endovascular management is often considered the primary treatment option for DAVMs in the cavernous sinus; for DAVMs of the transverse and sigmoid sinus regions, the combination therapy of

transarterial embolization and surgery provides a more effective treatment than either treatment alone. Embolization alone may be relatively ineffective in DAVMs of the tentorial incisura, however when used in conjunction with surgery may provide a slight advantage over surgery alone [110]. There is little evidence supporting the use of endovascular treatment in the management of DAVMs of the ACF, SSS, or middle cranial fossa (MCF) location.

One of the greatest problems with transarterial embolization is the high rate of incomplete occlusion due to revascularization of the lesion, particularly if not all feeding vessels have been embolized [151]. The theoretical benefit of transvenous embolization includes a greater likelihood of complete occlusion of the abnormal AV shunts [130]. However, the corollary is that although the transvenous approach may be effective in occluding the site of AV shunting, the draining veins and dural sinuses are thin-walled structures and may be perforated by catheters and guidewires [152].

Although stereotactic radiosurgery is claimed to avoid many of the potential complications of embolization and surgery, it is not completely risk-free. Transient neurological deficits due to treatment occur in up to 10% [153-155], and serious neurological complications have been reported [156]. Questions also remain regarding the long-term efficacy of occlusion following radiosurgery, with recurrences reported after complete angiographic obliteration [157].

3.6 Prognosis

For many years, the location of a DAVM was believed to be an important determinant of its behaviour [158]. Subsequently, more detailed studies have demonstrated that after accounting for the pattern of venous drainage, location has no direct correlation with the behavior or natural history of a particular lesion [106, 107, 134]. Instead, due to local venous anatomy, DAVMs in some locations (such as the ACF and tentorial incisura) are more likely to develop retrograde parenchymal venous drainage; it is this pattern of venous drainage that has been demonstrated to be predictive of aggressive behavior [106, 107, 159-161].

The pattern of venous drainage may be defined according to two commonly used classification systems [106, 107]: Borden type I, or Cognard type I and IIa are benign lesions with no retrograde parenchymal venous drainage; Borden type II and III, or Cognard type IIb, IIa+b, and III-V are aggressive lesions exhibiting various degrees of retrograde parenchymal venous drainage.

The natural history of DAVMs relates to the pattern of venous drainage. In general, the risk of intracranial hemorrhage for all DAVMs is approximately 1.8% per year [132]. However, DAVMs that demonstrate retrograde parenchymal venous drainage are associated with a more aggressive natural history [106, 107, 159, 160]. The risk of intracranial hemorrhage or non-hemorrhagic neurological deficit in DAVMs with retrograde parenchymal venous drainage is 15-30% per year, with an annual risk of death of 10-19% [162, 163]. When intracranial hemorrhage occurs, the effects can be devastating, with a 15-25% risk of death [132, 159, 164], and a 35% risk of rebleeding within 2 weeks if the DAVM remains untreated [164].

Effective treatment of DAVMs, with obliteration of all AV shunting, has been shown to result in reversal of neurological deficits [148, 165-172], including visual loss [173, 174]. However, complications can occur from all modalities of management (including observation alone), and progression of venous thrombosis and venous hypertension resulting in death can occur despite multiple attempts at intervention [175, 176].

Many published series report the initial post-treatment angiogram results as confirmation of angiographic obliteration, without performing delayed angiography. Recurrent DAVM, as well as development of new DAVM at sites remote from the initial lesion, can occur after complete obliteration [177-180]. In view of this finding, some authors recommend angiographic follow-up at least 1 year after treatment, to ensure that long-term occlusion has occurred [179]. Other forms of non-invasive angiography (such as CT or MR angiography) are becoming increasingly useful in the follow-up of these lesions.

3.7 Screening of relatives

There is currently no evidence to support the use of diagnostic imaging to screen for the presence of dural AVMs in asymptomatic patients.

4. Vein of galen malformations

4.1 Theories of pathogenesis

Vein of Galen malformations represent a particular subtype of intracranial vascular malformation, and consist of a single midline venous sac with a direct AV fistula within the wall. True vein of Galen malformations represent an embryonic malformation [181], with the malformation corresponding to the persistent fetal median prosencephalic vein, often in association with other abnormalities of arrested venous development [182]. Aneurysmal dilatation of an embryologically normal vein of Galen due to increased venous drainage from another vascular abnormality within its venous territory does not represent a true vein of Galen malformation. Although this type of aneurysmal dilatation has been classified as a type 4 vein of Galen malformation in the classification system of Yasargil [183], a descriptive term such as secondary vein of Galen aneurysmal dilatation is more informative [182, 184].

The true embryonic form of vein of Galen malformation is different from other pediatric DAVMs [105]. As well as having a different pathogenesis, one of the primary differences between DAVMs and vein of Galen malformations is the primary blood supply of the lesion [185]. In DAVMs the primary blood supply is that of the adjacent dura, whereas in vein of Galen malformations it is that of the adjacent brain parenchyma (arising from the fetal prosencephalic and mesencephalic arterial systems) [181]. Lasjaunias, *et al.* classified pediatric DAVMs into three types [105]: dural sinus malformations, infantile type dural arteriovenous shunts, and adult type dural arteriovenous shunts.

Dural sinus malformations and infantile DAVMs present in neonates and early childhood, and are more likely to represent a congenital abnormality in venous development. The adult type is less frequent, representing less than 1% of all pediatric intracranial AVMs; and when presenting in the pediatric population, tends to occur in older children [105].

4.2 Genetics

At present, the role of genetic factors in the formation of VOGM is unknown. Only 1 case of familial VOGM has been reported [186]. However, mutations in the RASA1 gene have been investigated in association with cutaneous capillary malformation-arteriovenous malformation syndrome, including two patients who also harboured VOGMs [187], raising the possibility that genetic influences may play a role in the development of these malformations.

4.3 Clinical features

Typically, neonates present with severe congestive cardiac failure (CCF), infants present with macrocephaly or hydrocephalus, and older children or adults present with seizures, headaches, or cranial neuropathies resulting from mass effect [186].

4.4 Diagnosis, including early detection

The diagnosis of VOGM is made after detailed clinical examination and investigation. Initial radiological examination includes transfontanel ultrasound and cardiac ultrasound (to assess for associated cardiac abnormalities), and MR Imaging of the brain. Angiography is not recommended in neonates unless urgent endovascular treatment is considered [188].The Bicetre Neonatal Evaluation Score [188] requires evaluation of cardiac, cerebral, respiratory, hepatic, and renal function in order to guide management decisions, and is used to triage neonates to either conservative management, or immediate or delayed endovascular management.

Non-invasive vascular imaging using contrast-enhanced CT angiography and MR angiography is becoming increasingly useful, particularly in neonates where the risk of catheter angiography is greatest. However, digital subtraction cerebral angiography is best for precise evaluation of vascular architecture in VOGMs [189].

Fetal ultrasound and MRI are useful for the antenatal diagnosis of aneurysmal malformations of the Vein of Galen, and allow for early management decisions to be made [190-192].

4.5 Treatment and prognosis

Many patients are not offered invasive treatment for their VOGM, usually due to poor cardiac or neurological condition at the time of diagnosis. Without treatment, VOGM is associated with a fatal outcome in >90% [193], usually from cardiac failure or neurological complications such as hydrocephalus.

Treatments strategies have evolved dramatically over the past decades, with series published before the year 2000 reporting a 15% mortality rate with endovascular management, and an 85% mortality rate with microsurgical management [193]. For this reason, surgery is rarely recommended as a first-line management option for VOGM. Although ventricular shunting may be required for the management of hydrocephalus in older children and adults, this may be avoided with early endovascular occlusion of the arteriovenous shunt in neonates and infants [194]. The published experience on stereotactic radiosurgery for VOGM is extremely limited [195].

Endovascular approaches to treatment are usually performed with the goal of obtaining complete exclusion of the malformation through a combination of transarterial and transvenous routes (with transarterial being the preferred route, and transvenous access only required in 2%) [194]. Multiple treatment sessions are usually required (average 2.4 sessions per child), and total or near-total occlusion was obtained in 55% of patients in this series.

Although published series in the past 10 years have not reported a change in the mortality rate significantly [193], the extensive experience reported from the Hospital de Bicetre, France, describes good clinical outcomes in 74% of patients and a mortality rate of 11% [194].

Outcome from endovascular treatment is highly dependent on the age of the patient at the time of presentation. Mortality rates as high as 50% have been recorded in neonates, with death rates around 7% in infants (<2 yrs) and 0-3% in children and adults undergoing treatment [193, 194].

4.6 Screening of relatives

There is no evidence to suggest that antenatal diagnosis of VOGM is associated with improved treatment outcomes, although it may assist with early referral to a center with experience in management of the complex cardiac and neurological issues facing these patients [192]. In spite of this, there is currently no evidence to support the use of diagnostic imaging to screen for the presence of VOMG in asymptomatic patients.

5. Capillary telangiectasia

5.1 Theories of pathogenesis

Capillary telangiectasias consist of multiple abnormally dilated capillary vessels, with normal intervening brain parenchyma. They are relatively common, rarely symptomatic, and are most commonly found in the region of the pons [196, 197]. They are traditionally considered to be congenital malformations, arising as a result of aberrant angiogenesis or failure of capillary involution during development [198]. This belief is based on the assumption that brain capillary telangiectasias are the same as cutaneous capillary malformations (or 'port wine stains') [29], although little evidence exists to support this theory of pathogenesis. Capillary telangiectasias have been reported to co-exist with developmental venous anomalies and cerebral cavernous malformations [198, 199], as well as developing after resection of a cavernous malformation [213]. This last case in particular indicates that *de novo* capillary telangiectasias may develop in adults, and suggests that these lesions may represent a spectrum of the same disease process.

5.2 Genetics

Although several genetic loci have been implicated in the development of cutaneous capillary malformations (including mutations of the RASA1 gene, located on chromosome 5q13-22, and implicated in Parkes-Weber Syndrome, a condition associated with cutaneous capillary malformations and brain AVMs) [187], very little is known about the role of genetic abnormalities in capillary telangiectasias of the brain.

5.3 Clinical features

It is very rare for capillary telangiectasias to present clinically; they are often found as an incidental finding at autopsy or during MR imaging for other unrelated conditions [197, 200]. Occasionally, they can present with hemorrhage or mass effect on surrounding structures, resulting in seizures, cranial nerve dysfunction, confusion, dizziness, visual disturbance, vertigo, tinnitus, or motor deficits [200, 201]. They have been implicated as a potential cause of non-aneurysmal perimesencephalic subarachnoid hemorrhage [202].

5.4 Diagnosis, including early detection

Brain capillary telangiectasias are not seen on CT, and are difficult to detect on MRI with standard T1- and T2- weighted imaging. However, they display mild homogenous enhancement with contrast material, and are often markedly hypo-intense on Gradient Echo sequences [200, 203]. They are not demonstrable on digital subtraction cerebral angiography.

5.5 Treatment

It is extremely rare for small brain capillary telangiectasias (<1 cm in maximum dimension) to present with symptoms, and the majority of cases do not require active treatment. Larger lesions may be symptomatic, and require surgical resection [200].

5.6 Prognosis

Capillary telangiectasias are benign lesions that usually do not cause neurological symptoms. In a large series of over 100 patients with brain capillary telangiectasias, only 2 patients were symptomatic, and 1 patient required surgical resection [200]. Other smaller series have reported on lesions where symptoms have improved with medical management of seizures, or have resolved spontaneously [201]. Rarely have reports described progressive neurological symptoms or death from unruptured capillary telangiectasias [204, 205]. Although hemorrhage from a capillary telangiectasia has been reported [202], the risk of hemorrhagic complications from these lesions is not known.

5.7 Screening of relatives

There is no evidence to support the use of diagnostic imaging to screen for the presence of capillary telangiectasias in asymptomatic patients.

6. Cavernous malformation

6.1 Theories of pathogenesis

Cavernous malformations (cavernomas, cavernous hemangioma) consist of abnormal, thin-walled sinusoidal vascular channels. There is not generally any brain parenchyma between the vessels and there is lack of basement membrane, smooth muscle, elastin, and adventitia [228,229]. Most cases have either imaging or pathological evidence of prior hemorrhage and organizing thrombus; calcification is also frequently seen.

As with other vascular malformations described in this chapter, there was an initial assumption of a congenital origin, which has recently been brought in to question. New malformations have been documented in familial and non-familial cases and in regions of brain treated with radiotherapy for other conditions [228]. Genetic abnormalities have been identified in patients with familial cavernous malformations. The genes identified code for proteins that are important for vascular development.

Another proposed mechanism of cavernous malformation development is venous hypertension, particularly in cases associated with developmental venous anomalies [232]. The proposal is that chronically raised venous pressure influences the development of cavernous malformations or may at least predispose to their recurrence after surgical removal.

6.2 Genetics

Cavernous malformations occur in all races and there is no sex predilection. The prevalence is approximately 0.5% [228], although the rate is higher in the Hispanic population. In some familial forms there is almost 100% penetrance [228]. Almost all Hispanic patients and 40% of Caucasian patients with familial cavernous malformations have a constitutional defect in the KRIT1 gene, also known as CCM1 [230]. KRIT1 codes for a protein that plays an important role in blood vessel development and may play a role in blood-brain-barrier formation. Over 100 mutations of the KRIT1 gene have been identified that are associated with the development of cavernous malformations.

Defects in other genes, (CCM2 and CCM3), are also associated with cavernous malformation development. CCM2 and CCM3 code for proteins that are thought to be important in the signaling between neurons and developing vascular cells in the central nervous system. Many different mutations of these genes have been identified in cavernous malformation patients, accounting for approximately one third of familial cases [231].

6.3 Clinical features

Cavernous malformations account for up to 10% of central nervous system vascular malformations and the mean age at presentation is approximately 40 [228]. In familial cases there are often multiple lesions, whereas sporadic cases usually have only one lesion.

Presentation is with headache or neurological deficit from hemorrhage, or with seizures. In contrast to AVMs, hemorrhages from cavernous malformations are generally not life-threatening. Neurological deficits occur when the lesions are in eloquent regions of the brain such as the brain stem or primary motor cortex. The annual risk of hemorrhage has been estimated at 4%, with higher risks accompanying familial cases, after an initial clinical hemorrhage, or for lesions located in the brain stem [228]. There may be a higher risk during pregnancy.

6.4 Diagnosis, including early detection

Catheter angiography will often not reveal cavernous malformations. Subtle hyperdensity may be seen on non-contrast CT, although even a contrast scan will not detect many lesions. The hemosiderin deposition resulting from prior hemorrhages makes MRI an exquisitely

sensitive diagnostic technique. In addition to making the diagnosis, MRI is important for determining the location of the lesion and its relationship to pial or ependymal surfaces, which are important factors in surgical decision-making.

6.5 Treatment

Surgical excision is the only effective treatment for cavernous malformations; there is no role for endovascular therapy and there is little evidence supporting the efficacy of radiosurgery. The indications for surgery are to prevent hemorrhage and to improve control of seizures. Excision of lesions in asymptomatic patients is usually not justified. Surgery is reasonable for lesions in the brain stem that have bled at least once, and where the lesion comes to either a pial or ependymal surface. If seizure control is the main concern, it may be preferable to proceed with surgery within the first year after presentation, as there is some evidence that this improves seizure outcomes [228].

6.6 Prognosis

Left untreated, cavernous malformations remain at risk of hemorrhage. Neurological deficits are particularly common after hemorrhage in the brain stem and the effects are cumulative with each hemorrhage. Surgical excision of cavernous malformations relieves mass effect on surrounding brain and may be effective in controlling seizures, especially if surrounding hemosiderin-stained tissue is removed. Unfortunately, removal of lesions in the brain stem does not necessarily eliminate the risk of hemorrhage: there is a growing awareness of a moderately high rate of recurrence in this region and the spinal cord [233]. Whether recurrence is related to further growth of residual malformation or development of a new lesion remains to be determined.

6.7 Screening of relatives

Although familial forms of the condition are well recognized, there is not a clear indication for screening relatives of affected patients. Since there is not usually an indication for treatment of asymptomatic patients with cavernous malformations of the brain, we do not generally recommend screening. For relatives in familial cases who request screening, it is reasonable to obtain an MR scan.

7. Developmental venous anomalies

7.1 Theories of pathogenesis

Developmental venous anomalies (also known as developmental venous malformations and venous angiomas) are composed of a radially-arranged cluster of venous radicles converging into a larger, mature venous channel [206, 207]. The venous structures are angiographically mature, and express normal structural proteins in their walls [208].

There are several broad theories of pathogenesis for DVAs, and all assume that they form *in utero*. The first theory is that DVAs represent anatomical variants formed by the opening of transhemispheric anastomotic pathways between the superficial venous system and the deep venous system of the brain in response to hemodynamic demand [209]. In this model, the DVA is a normal structure, performing a normal physiological function.

Other theories propose that DVAs form in response to thrombosis or occlusion of normal parenchymal veins, or as a result of abnormal fetal angiogenesis [210, 211]. These theories consider the DVA to be a response to an antenatal pathological event rather than a normal anatomical variant [212].

7.2 Genetics

Developmental venous anomalies are associated with other cerebral vascular malformations, in particular cerebral cavernous malformations, in up to 40% of cases [206]. Isolated case reports have described the temporal development of a cerebral cavernous malformation in the region of a DVA; prompting the suggestion that regional venous hypertension may serve as a common pathogenetic mechanism [213, 214]. Familial cavernous malformations are unlikely to be associated with the presence of a DVA, whereas a DVA is likely to co-exist with a sporadic CCM in almost half of cases [215], countering the argument that a simple genetic defect is responsible for the co-existence of these two vascular malformations.

Intracranial DVAs are also associated with peripheral vascular abnormalities, and are present in 20% of patients with cutaneous venous malformations [207]. In particular, DVAs have been reported in patients with blue rubber bleb nevus syndrome and sinus pericranii, prompting the suggestion that sinus pericranii should be considered the extracranial manifestation of a common spectrum of venous malformations [216, 217].

The vast majority (about 95%) of cutaneous venous malformations are sporadic, but a small proportion of cutaneomucosal venous malformations are inherited in an autosomal dominant pattern. The genetic defect responsible for this form of venous malformations is a mutation in the TEK gene (encoding for the angiopoieten receptor, TIE2; located on chromosome 9p21) [218, 219]. Despite the potential for a link between these malformations and DVAs, there is no evidence to support the hypothesis that this gene defect is responsible for the development of intracranial DVAs.

Intracranial DVAs have also been reported in associated with the spectrum of vascular anomalies occurring in patients with mutations of the PTEN gene [220].

7.3 Clinical features

Developmental venous anomalies are the most common cerebral vascular malformation, with a prevalence in imaging series of 0.5-0.7%, and in autopsy series of 2.6% [207]. The vast majority are asymptomatic, and are often found as an incidental finding during imaging for other unrelated conditions.

The most common reason for neuroimaging in patients with a DVA is headache; however, an exact causal relationship is often difficult to prove, as symptoms may resolve over time without treatment of the vascular anomaly. Similarly, in patients presenting with seizure or neurological deficit, there is often no direct correlation between the anatomical location of the DVA and the neurological symptoms [207].

The risk of hemorrhage from a DVA is low, with retrospective series reporting an annual hemorrhage rate of 0.6%, and prospective series reporting an annual hemorrhage rate of 0.7% (with a symptomatic hemorrhage rate of 0.3%) [221]. Cerebral edema, venous

infarction, and hemorrhage may occur following stenosis or thrombosis of the draining vein of the DVA [212, 222].

7.4 Diagnosis, including early detection

Developmental venous anomalies are rarely visible on non-contrast CT imaging, unless associated with a cavernous malformation. Following the administration of intravenous contrast, the DVA is visualized as a collection of venous tributaries or 'caput medusa' draining via an enlarged draining vein [214]. CT perfusion studies may be useful in determining the hemodynamic alterations present as a result of the altered regional venous drainage [223].

Similarly, DVAs may be seen on T1- and T2-weighted MR imaging, but are best visualized on gadolinium-enhanced T1-weighted imaging. Gradient echo sequences may show a ring of hypointensity if previous hemorrhage or an associated cavernous malformation is present. MR imaging is also valuable for the detection of parenchymal abnormalities often associated with DVAs [214].

Conventional digital subtraction angiography shows normal arterial and capillary phase, with typical venous phase demonstrating the 'caput meduase' of dilated medullary veins converging upon an enlarged subcortical or subependymal draining vein [207, 224]

7.5 Treatment

Traditionally, neurosurgeons have understood that DVAs represent a variant of normal venous drainage, and as such should never be a target for treatment [209]. However, others have challenged this belief, suggesting that removal of CCM without removal of the underlying DVA results in recurrence of the CCM in up to one third of patients. Particularly in this group of patients, cautious coagulation and dissection of the large transcerebral DVA may be considered [225].

We advocate a conservative approach, and recommend that surgical treatment never be offered to patients with asymptomatic DVAs. In the setting where hemorrhage has occurred, then evacuation of the hematoma may be considered, but surgical disruption of the DVA should be avoided. Associated cavernous malformations should be completely excised, with preservation of the anomalous venous drainage wherever possible. We do not believe that sufficient evidence exists to support the routine removal of DVAs to prevent the development of recurrent cavernous malformation.

7.6 Prognosis

Most of the evidence relating to DVAs suggests that they are a variant of normal venous drainage; they are a normal structure, performing a normal physiological function. Once considered a rarity, with a high propensity for hemorrhage, they are in fact the most frequently encountered vascular malformation, occurring in up to 3% of the population [226]. Developmental venous anomalies themselves have a very low risk of hemorrhage, with prospective series reporting a symptomatic hemorrhage rate as low as 0.3% [221]. They are, however, associated with the development of other vascular malformations (in particular cavernous malformation), which increase the risk of symptomatic hemorrhage to as high as 6% per year [227].

7.7 Screening of relatives

There is currently no evidence to support the use of diagnostic imaging to screen for the presence of DVAs in asymptomatic patients. Although of little clinical benefit, there may be research interest in screening relatives of patients with blue rubber-bleb nevus syndrome for intracranial venous anomalies, in order to improve our understanding of the genetic and molecular influences responsible for the development of vascular malformations in these patients.

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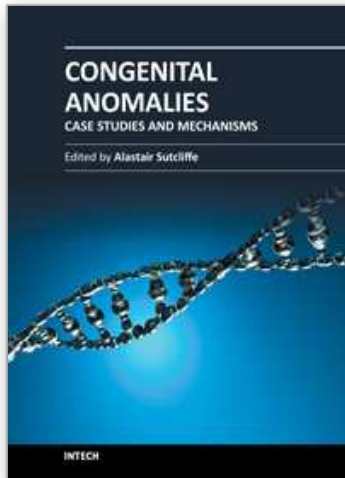
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Edited by Dr. Alastair Sutcliffe

This book is in essence a collection of essays which are state of the art in their respective areas of knowledge. They inform the reader of all sorts of mechanistic considerations when developing understanding of issues surrounding the origins of congenital abnormalities. These chapters are written by world renown authorities in this area of science and represent a wide range of expertise from a clinician perspective, through to genetic mechanisms. Unlike some books which take a formal textual, somewhat plodding way through pathophysiology here instead we have cut through chapters in which the student , or scientist or medic is lead to understand just how complex the origins can be via examples from different parts of the body. With the erudite chapters are relevant tables and other diagrams to help clarify the text . These chapters represent a starter text for the stimulus for further knowledge of what is an increasingly important area of human health.

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