Introduction: Non-atherosclerotic Cerebrovascular Disorders

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Non-atherosclerotic cerebrovascular disorders are considered to occur less frequently than those caused by embolic or thrombotic disease. Such sporadic disorders resulting from direct effects on the cerebral or peripheral vasculature include hypertensive small vessel disease, vascular inflammatory conditions, aneurysms and arteriovenous malformations. Remarkably, some of these are also inherited in an autosomal dominant manner and appear to entail degeneration or abnormal differentiation of blood vessel wall elements such as smooth muscle, endothelial cells, pericytes and the perivascular nerve plexus. Two intensively investigated examples of these include the cerebral amyloid angiopathies and distinct primary arteriopathies such as CADASIL. The identification of novel genes associated with the hereditary forms of cerebrovascular disorders has been invaluable to understanding of the pathogenesis and management of sporadic disease.

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Aging-related atherosclerotic disease is the principal cause of cerebrovascular disease with ischemic strokes in man. While this is highly important in view of the profound morbidity and mortality it entails, a large number of disorders encompassing both ischemic and hemorrhagic lesions arise from primary or secondary pathologies affecting brain vessel walls or the systemic circulation (13; Table 1). Sporadic and genetically determined non-atherosclerotic cerebrovascular disease may also result from metabolic dysfunction (8, 12). Examples of these include such diverse conditions as MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes), Ehlers-Danlos syndrome type IV, Marfan's syndrome, neurofibromatosis type 1, Fabry's disease and polycystic kidney disease. These too produce brain vascular pathology that may have repercussions upon local or more widespread cerebral perfusion and neuronal function.

The state of the art reviews in this symposium concentrate on recent developments in cerebrovascular disorders with different etiologies. They include the cerebral amyloid angiopathies (24), hypertensive small vessel disease (17), and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy or CADASIL (14). Cerebral amyloid angiopathy (CAA) most often occurs in the elderly. However, familial forms of CAA resulting in ischemic and hemorrhagic infarcts or oligemia appear the most studied among the hereditary cerebrovascular disorders (13). The systematic study of the CAAs has proven valuable in understanding cerebral amyloidosis as well as vascular function.

Hereditary forms of stroke unrelated to the amyloid angiopathies but presenting with strokes or transient ischemic attacks are also apparent. Interestingly, for the first time the elucidation of CADASIL has provided evidence for the existence of familial stroke syndromes caused by mutant genes predominantly expressed in vascular smooth muscle cells (14). CADASIL currently emerges as the most common form of autosomal dominant inherited stroke leading to progressive dementia (Table 1). However, other hereditary forms of leukoencephalopathy with phenotypes similar to Binswanger's disease and CADASIL linked to loci on chromosomes other than 19 appear to exist (6, 12, 29). The identification of primary leukoencephalopathies will be of value in understanding the pathogenesis of white matter disease associated with late-onset dementias.

In addition to CADASIL, occlusive conditions such as hereditary endotheliopathy, with retinopathy nephropathy, and stroke (HERNS; ref 11), fibromuscular dysplasia (7) and moya-moya disease (1) are also of increased interest. While 90% of moya-moya disease appears to be sporadic, it is noteworthy that at least 3 different gene loci have been proposed to be associated with the familial moya-moya syndromes (9, 10, 32). Moya-moya is an uncommon cause of hemorrhagic or ischemic stroke in children and young adults. The prevalence of moya-moya is about 3 per 100 000 in Japan, higher than in any other country, but the disease also occurs in Western countries. The pathology is char-

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Major disorder groups	Type(s)	Key Clinical Features			Main Pathological Features			
		CH (ICH/ SAH)	Infarcts	CI or dementia	VSMC changes	EC changes	WMLs	Other features
Cerebral amyloid angiopathies (CAAs)	Sporadic: Ageing-related Familial forms: HCHWA British, Danish and Iowa dementias.	+++ (ICH)	++	+++	+++	+++	++	Diffuse plaques; NF Pathology in some
Non-atherosclerotic stroke disorders	Hypertensive encephalopathy	++	+++	++	+++	++	++	Basal lamina changes
	CADASIL	-	+++	+++	+++	++	+++	Granular osmiophilic deposits
	Hereditary strokes not linked to Notch 3	+	+++	+++	++	++	+++	Lacunes
Vasculopathies and non-amyloid angiopathies	Familial: HERNS (hereditary endotheliopathy with strokes)	-	++	+	++	++++	++	Retinopathy; Nephropathy, proteinuria
	Familial: Cerebroretinal vasculopathy	-	++	++	+++	++	+++	Retinal EC changes
	Sporadic moya-moya syndrome Familial moya-moya	-	+++	++	+++	++	+++	Stenosis; arterial fibrous thickening, aneurysms
Vascular malformations and telangiectasias	Sporadic arteriovenous malformations; capillary teleangiectasis Familial: Cavernomas (some)	++	+	+	+++	+++	+ (focal)	Lack of intervening parenchyma (cavernomas)
	Hemorrhagic teleangiectasias (hereditary)	++	+	?	+++	+++ (no formed)	+ +	Dysplasia Aneurysms
Aneurysms	Saccular (berry) aneurysms (sporadic and familial forms)	++ (SAH)	+	?	++	++	+	Formed at branching arteries
Vasculitis	Non-infectious: GCA, PACNS, Takayasu's Infectious: bacterial, viral	-	±	?	+++	++	-	Presence of inflammatory mediators and fibroblasts

Table 1. Non-atherosclerotic cerebrovascular disorders as causes of strokes and cerebral hemorrhages.

Most disorders manifest as both sporadic and familial disease. Chart compiled from Kalimo et al (13); and Kalaria (12). Abbreviations: CADASIL, cerebral autosomal arteriopathy with subcortical infracts and leukoencephalopathy; CH, cerebral hemorrhage; CI, cognitive impairment; EC, endothelial cell; GCA, giant cell arteritis; HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; HCHWA, hereditary cerebral hemorrhage with amyloidosis; ICH, intracerebral hemorrhage; NF, neurofibrillary; PACNS, primary angiitis of the central nervous system; SAH, subarachnoid hemorrhage; VSMC, vascular smooth muscle cells (degenerative or proliferative); WMLs, white matter lesions.

acterized by progressive bilateral stenosis of the internal carotid and basal brain arteries involving the proximal portions of the anterior cerebral artery and middle cerebral arteries at the circle of Willis. These vessels are replaced by a meshwork of small collateral vessels, which may bear microaneuryms or false aneurysms that can be sources of intracranial hemorrhage (13). Microscopic findings suggest segmental narrowing and thickening of the intima and media, proliferation or in severe cases degeneration of smooth muscle cells and tortuosity of the internal elastic lamina as well as abnormalities in smooth muscle cells (1). In this context, here we briefly review two examples where advances in molecular genetics rather in conjunction with pathological observations have enabled further dissection of well-known non-atherosclerotic vascular diseases such as vascular malformations and intracranial aneurysms.

Vascular Malformations

Intracranial vascular malformations may include several classes of lesions, including arteriovenous malformations, Vein of Galen arteriovenous fistula or aneurysm, cerebral cavernous malformations (CCM), capillary teleangiectasis, venous malformations,

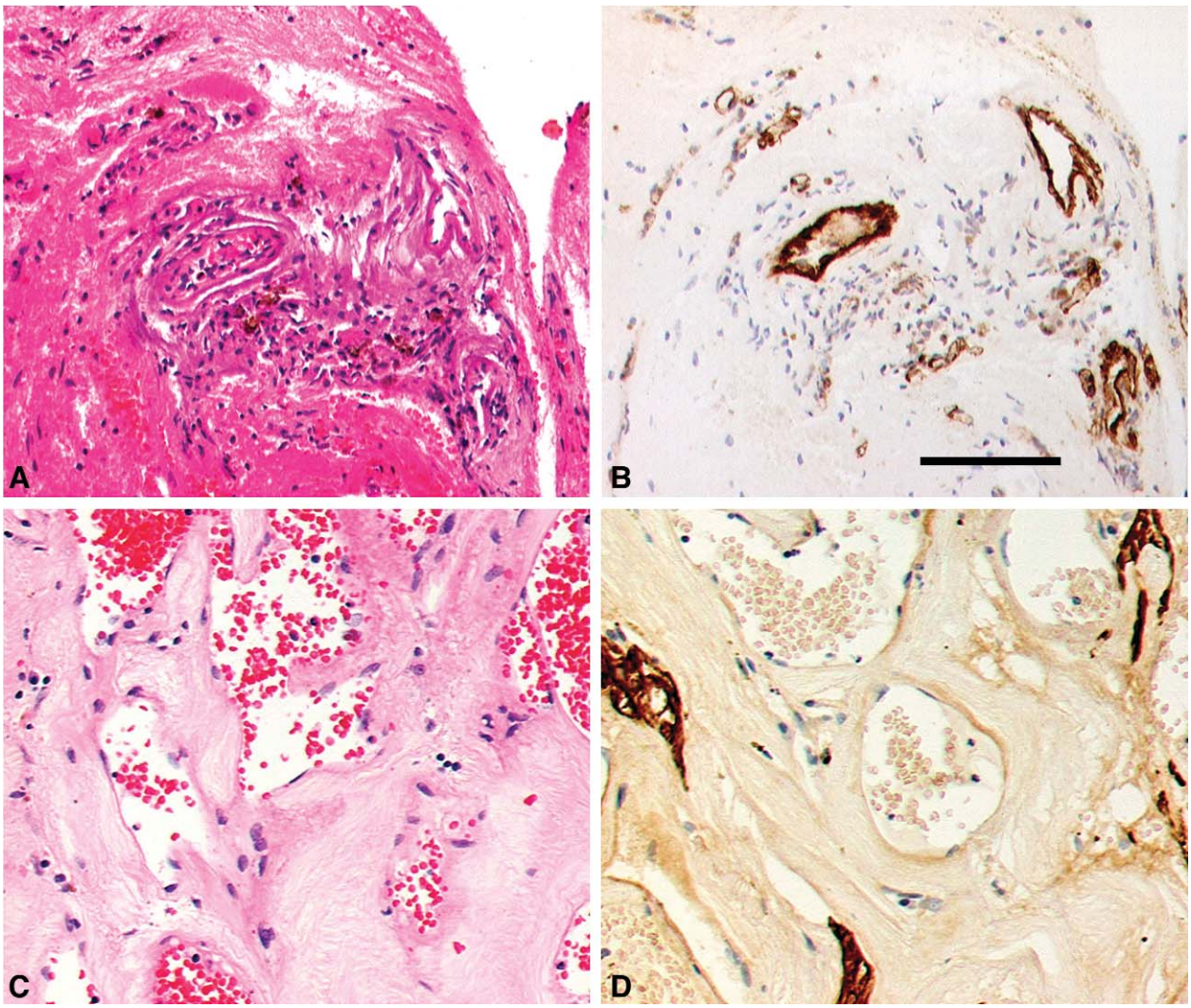

Figure 1. Neuropathology of vascular malformations: **A-D** show two different cases with CCM in the temporal (**A, B**) and parietal lobes (**C, D**). **A** and **C** demonstrate that CCM are composed of closely apposed dilated vascular channels with absence of intervening brain parenchyma in H & E stained sections. **B**, shows an adjacent section stained for α-actin, with characteristic reduction of smooth muscle cells (scale bar = 200 μm). Panel **D**, shows a gliotic response (brown) revealed with antibodies to glial acidic fibrillary protein.

angiodysplasia and aneurysms and hemorrhagic teleangiectasia (2, 4, 13). The main feature of arteriovenous malformations (AVMs) is the presence of arteriovenous shunting through a compact collection of coiled and tortuous vascular connections that connect feeding arteries to draining veins (20). The nidus of an AVM comprises multiple vascular lesions as enlarged capillary cavities or vascular channels. The absence of intervening parenchymal brain tissue and capillaries is characteristic of cerebral cavernous hemangiomas or malformations (CCMs) (Figure 1). The usual presentations of arteriovenous malformations is with seizures, headache, hemorrhages, and progressive neurological deficits. Recent estimates suggest they account for 1 to 2% of all strokes and 9% of subarachnoid hemorrhages (2, 4, 13).

CCM are perhaps the most common amongst vascular malformations and are believed to occur congenitally but become symptomatic after 20 years of age. The prevalence of CCMs is estimated to be 0.5% in the general population although they may be inherited in an autosomal dominant fashion in as many as 50% of cases. CCM may occur anywhere in the brain including the leptomeninges but are common in the subcortical

white matter, internal capsule and pons. Histopathological examination shows intervening cells within the nidus to exhibit chronic reactive changes and appear non-functional. Smooth muscle cells often appear hypertrophic and hyperplastic (1). If hemorrhage has occurred the surrounding brain parenchyma will show evidence of gliosis and hemosiderin (Figure 1).

Recent advances suggest 3 different chromosomal loci at 7q, 7p and 3q to be associated with familial CCM (16, 26, 33). The locus at 7q was recently identified by linkage analysis of several Hispanic American families (designated CCM1). This locus was subsequently identified to be a single gene whose protein product is KRIT1. Interestingly the brain exhibits the highest level of *KRIT1* gene expression (33). Single missense mutations in *KRIT1* co-segregate with CCM1 locus also in non-Hispanic families. While there is also a common disease haplotype in the Hispanic American families suggesting a founder effect in these, this is not true in Caucasian families. Analysis of the *KRIT1* gene has revealed up to 10 different mutations that predominantly fall into 3 types, namely frameshift, premature stop codon, and splice site mutations, all of which confer loss of function (26). The KRIT1 protein interacts with Rap1A (also known as KREV1), which antagonises the Ras family of GTPases but its exact function in angiogenesis or vasculogenesis remains unknown.

Like CCM, hereditary hemorrhagic teleangiectasia (HHT) is an autosomal dominant disorder associated with vascular dysplasia and recurrent hemorrhages (18, 19). Whether the vascular pathology evident in the CNS as well as other systems is vastly different from arteriovenous malformations in the absence of an intervening capillary network is unclear. Mutations in 2 different genes, endoglin and activin-like kinase receptor-1 (ALK-1) localised on chromosome 9 and 12 co-segregate with the disease (see original references in 19). Both genes belong to the transforming growth factor (TGF)-β receptor family of proteins and are expressed in endothelial cells of capillaries, arterioles and even venules. Endoglin and ALK-1 are found in a ligand-independent TGF-β receptor complex indicating that they share a common signaling pathway. Some 30 different mutations have been identified in the extracellular domain of endoglin, the majority of which cause frameshift or premature termination codons. It is predicted that the missense mutations result in misfolding of the receptor protein resulting in no cell surface expression whereas other mutations cause HHT1 either through haploinsufficiency or dominant-negative protein interactions (18).

Intracranial Aneurysms

Ruptured aneurysms are the most common cause of subarachnoid hemorrhages (5, 31). Saccular or berry aneurysms, which usually form at vessel junctions, are the most common among intracranial aneurysms. Aneurysms are most often present on the circle of Willis, usually its anterior portions. They tend to rupture when they grow beyond 5 mm in diameter. The structure of vessel cellular elements as well as their innervation is completely disrupted (23). Genetic factors also appear involved in the etiology and pathogenesis of intracranial aneurysms (25, 27). Familial intracranial aneurysms are relatively common and well-documented in several hundred families world wide. They may cause up to 20% of subarachnoid hemorrhages (12, 13). Intracranial aneurysms often occur in familial polycystic kidney disease and several other connective tissue disorders such as Ehlers-Danlos syndrome type IV, Marfan's syndrome and neurofibromatosis type 1. Current advances suggest genetic heterogeneity of intracranial aneurysms and there are likely to be a few candidate genes (30) involved in their inheritance. Thus far polymorphisms in 2 candidate genes have been widely tested. There is some evidence to suggest the insertion allele (I) of the angiotensin converting enzyme gene is over-represented in patients with intracranial saccular aneurysms (15) although this is not a consistent finding (28). Interestingly, hypertension and multiple aneurysms were the most frequent clinical features associated with the homozygous insertion of a 6-base allele in intron 7 of the endoglin gene, which is associated with HHT1.

Vasculitis

Cerebrovascular diseases may also result from acute and chronic inflammation of the vasculature. The majority of vasculitis in the CNS are non-infectious, manifesting as primary inflammation evident in Takayasu's arteritis, giant cell arteritis or primary angiitis (Table 1) or as secondary disease resulting from systemic conditions such as systemic lupus erythematousus, polyarteritis nodosa, Churg-Strauss syndrome and Behçet's disease (3). However, vasculitis, albeit less commonly, may also arise from bacterial, viral, or fungal infections (13).

Whether the cause is genetic or not, in each of these disorders vascular structure and function are compromised through the degeneration of vessel wall component cells, especially smooth muscle or endothelium. Such cellular abnormalities may result from accumulation of toxic gene products or disturbances in their proliferation and differentiation. Changes in smooth muscle cells and

the endothelium may further induce secondary pathologies including thrombosis, altered hemodynamics and increased diapedesis that would affect vascular perfusion and permeability functions. Disruption in vessels may also impinge on the integrity of the perivascular nerve plexus, particularly in the larger vasculature, and affect vascular tone and vessel wall integrity. Depending on the degree of vascular disruption these effects may induce discrete infarcts or cause oligemia that ultimately determine the degree of perivascular damage and neuronal viability within the vascular bed and connecting brain regions.

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