STROKE IN YOUNG ADULTS: CEREBRAL ARTERIOPATHIES

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Introduction

Cerebral arteriopathies are among the most challenging group of conditions encountered by the vascular neurologist. They are collectively the most common cause of stroke, accounting for 20-35% of strokes in young adults(1-2) and over 50% in children(3). In older adults, atherosclerosis alone accounts for 20%-50% of stroke(4) and lipohyalinosis another 15%.

In this lecture, I will mainly focus on non-atherosclerotic cerebral arteriopathies that most commonly affect young adults (**Table**). Pediatric cerebral arteriopathies such as transient cerebral arteriopathy and post-varicella angiopathy are beyond the scope of this talk. Intracranial atherosclerosis, Binswanger's disease, cerebral amyloid angiopathy, and other forms of chronic microvascular ischemia that typically affect the elderly, will not be discussed. One exception however is *premature cerebral atherosclerosis*, because accumulating evidence from several large studies published in the past 5 years suggests that the incidence of risk factors for premature atherosclerosis is increasing in young adults, and that premature atherosclerosis is a major factor affecting outcome and the risk for recurrent stroke in young adults(5-11).

Table: Non-Atherosclerotic Cerebral Arteriopathies

1. Carotid and vertebral artery dissection
2. Reversible cerebral vasoconstriction syndromes (RCVS)
3. Moyamoya disease and moyamoya syndrome
4. Inflammatory / immunological vasculitis *(e.g. primary angiitis of the CNS, giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, scleroderma, systemic lupus erythematosis, Behcet's disease, Churg-Strauss syndrome, Kohlmeier-Degos disease, Eale's disease, Spatz-Lindenberg disease, vasculitic cerebral amyloid angiopathy)*
5. Infectious arteritis *(e.g. TB, syphilis, cysticercosis, herpes zoster, bacterial meningitis)*
6. Genetic / Inherited / Developmental anomalies *(e.g. Fabry's Disease, fibromuscular dysplasia, dolichoectasia, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal-recessive arteriosclerosis with subcortical infarcts and leukoencephalopathy (CARASIL), sickle cell disease, Osler-Weber-Rendu syndrome, Ehlers-Danlos syndrome type IV, Marfan syndrome, Neurofibromatosis type 1, TREX-1 mutation, osteogenesis imperfecta, pseudoxanthoma elasticum, arteriovenous and cavernous malformations, venous anomalies)*

Non-atherosclerotic cerebral arteriopathies deserve special attention because their natural history, prognosis, and treatment differ considerably from atherosclerosis. They accounted for 5.6% of strokes in the Baltimore-Washington Co-operative Young Stroke Study(2) and 19% of strokes in a population-based epidemiological survey in Sweden(12). They can be classified according to their etiology (**Table**); however from the standpoint of diagnostic approach, it is important to first distinguish medium-vessel from small-vessel cerebral arteriopathies(13). Medium-vessel arteriopathies induce visible abnormalities on angiography, while small-vessel arteriopathies affect distal vessels that are beyond the current resolution of angiography. Some arteriopathies, e.g. the reversible cerebral vasoconstriction syndromes (RCVS) and primary angiitis of the central nervous system (PACNS), can affect both the medium and the small vessels. The final clinical manifestation of cerebral arteriopathies may be similar (ischemic or hemorrhagic stroke, seizures, brain edema) however the key to diagnosis rests on the detection of associated signs and symptoms, and recognition of their clinical and radiologic features.

Approach to Diagnosis

A multi-disciplinary approach involving neurologists, neuroradiologists, rheumatologists, geneticists, and others, is required for the appropriate diagnosis and management of cerebral arteriopathies.

The diagnosis of a *small-vessel cerebral arteriopathy* requires a high index of clinical suspicion, astute neuroradiology interpretation, and a careful skin, eye, and organ system examination. Patients typically develop recurrent strokes from small-sized infarctions or micro-hemorrhages(14), and often have chronic headaches, cognitive deficits, or psychiatric manifestations. MRI findings of scattered small-vessel infarcts or micro-hemorrhages with or without white matter lesions should raise suspicion for small-vessel arteriopathy. Genetic arteriopathies may be suggested by funduscopic abnormalities e.g. retinal arterioloar irregularities (CADASIL, TREX-1) or branch retinal artery occlusions (Susac's syndrome). Skin examination may reveal characteristic lesions, e.g. atrophic white papules in Dego's disease, or livedo reticularis in systemic lupus erythematosus. Abnormal cerebrospinal fluid (CSF) examination results are common in cerebral vasculitis and infectious arteriopathies. Several small-vessel arteriopathies (e.g. CADASIL) have established diagnostic criteria(15) or can be confirmed with specialized tests such as skin or brain biopsy, or genetic, immunological, or microbiological tests. Some small-vessel arteriopathies are diagnosed solely with clinical-imaging correlation, e.g. lipohyalinosis in patients with chronic hypertension, a well-defined lacunar stroke syndrome, and a corresponding small cerebral infarction in the distribution of a 'penetrator' artery. Others such as PACNS continue to pose diagnostic challenges because definitive diagnostic tests like brain biopsy are often false-negative, and tests like CSF examination and angiography have low specificity.

Medium-artery and large-artery cerebral arteriopathies typically come to attention when CT-angiography or MR-angiography (CTA or MRA) performed during a routine stroke or headache evaluation show ectasia, beading, or irregularities of the intracranial vessels. Common clinical features of medium-sized arteriopathies include recurrent sudden-onset, severe "thunderclap" headaches (which is pathognomonic for the reversible cerebral vasoconstriction syndromes or *RCVS*); stroke in the setting of recent headache, infection, recent pregnancy, vasoconstrictive medication exposure or illicit drug use; stereotyped transient ischemic attacks; or imaging findings of unilateral deep borderzone infarcts(16). As with small-vessel arteriopathies, the skin and eye examination can be informative, e.g. ectopia lentis (Marfan's syndrome); iris hamartomas, optic nerve tumors and café au lait spots (Neurofibromatosis-1); or cataracts, corneal opacities and angiokeratomas (Fabry's disease).

Unfortunately in the absence of validated diagnostic criteria or confirmatory tests, the diagnosis and management of arteriopathies remains variable and uncertain. Patients with suspected cerebral arteriopathy typically undergo a battery of expensive diagnostic tests, most of which have relatively low sensitivity and specificity, often culminating in a brain biopsy or empiric treatment for conditions like cerebral 'vasculitis', which is not without risks. Ongoing studies are evaluating whether arteriopathies can be diagnosed on basis of different patterns of arterial contrast enhancement on high-resolution (3-Tesla) MRI(17-19). Prospective studies are needed to refine diagnostic criteria and develop treatment algorithms, as well as investigate the safety of thrombolysis in young patients with stroke from cerebral arteriopathies(20).

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In this lecture, I will inform you about the main epidemiological, clinical, and imaging features of several important cerebral arteriopathies. I will address the approach to diagnosis and discuss management issues. It will not be possible to cover every cerebral arteriopathy in-depth in the allocated time. Selected references are presented below.

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