Progress in the Genetics of Cerebrovascular Disease: Inherited Subcortical Arteriopathies

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We have much to discover regarding the etiology of cerebral infarction, as the commonly recognized risk factors, such as hypertension, diabetes, and atrial fibrillation, account for only a small proportion of stroke.

Genetic factors are clearly important. Substantial genetic components underlie hypertension and diabetes. However, as contributors to the known risk factors for stroke, they are encompassed within that part of stroke risk that has already been identified. The importance of otherwise unspecified genetic factors in vascular disease has been illustrated by coronary heart disease, in which having an affected first-degree relative may increase an individual's risk tenfold. The evidence of a role for family history in cerebral infarction is less impressive, but present. Even taken together, the many genetic conditions that predispose to stroke in a Mendelian (single-gene) fashion explain few infarcts. Single-gene diseases that specifically and directly affect the cerebral circulation are seemingly limited, to date, to Dutch and Icelandic amyloid disease, and these present primarily with intracerebral hemorrhage, not infarction.

Bousser and Tournier-Lasserve report the proceedings of an international workshop on cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which has an autosomal dominant pattern of inheritance. The condition has now been localized to chromosome 19q12 in two unrelated families, thus providing a marker for the condition. CADASIL presents clinically in the third to seventh decades, although some pedigrees have a consistently later age of onset than others. It begins with recurrent stroke or, less commonly, transient ischemic attacks. Complete remission after the early episodes may be seen. After several years the pattern of progression may alter. Recurrent, discrete events may cease and be replaced by a steadily progressive pseudobulbar palsy and subcortical dementia. Cer-ebellar signs may occur. Traditionally accepted vascular risk factors are conspicuously absent. Migraine-like headache and psychiatric complaints, particularly depression, are associated with the condition. Given the frequency of migraine in the general population, care must be taken when including migrainelike headache as part of this syndrome. The case series reported in the workshop proceedings had a highly variable prevalence of migraine. Others (Verin) identify them with great frequency and still others (Chabriat, France) with an intermediate frequency. Depression is common in early dementia, and it may be more unique to this illness than to other dementias. These questions need prospective, critical analysis to avoid the development of an inaccurate phenotype and consequent misdiagnosis. A variety of other conditions, including the coagulopathies, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes), Fabry's disease, abnormal lipoproteinemia, cerebral amyloid angiopathy, and homocystinuria, have all been ruled out in these pedigrees.

The histopathology within the white matter is consistent. The most notable changes are multiple small infarcts in the basal ganglia, thalamus, periventricular white matter, and pons. There is variable cortical and central white-matter atrophy with diffuse myelin loss and pallor of the hemispheric white matter. Other ischemic changes include ischemic cell changes in the third cortical layer of the frontal and temporal cortex, with neuronal loss and astrocytic proliferation. These changes are closely reminiscent of those described in cases of subcortical ischemia associated with hypertension, and some aspects of the histopathology are similar to those described in leukoaraisis, especially the white-matter atrophy with diffuse myelin loss. The vascular changes are widespread but are most prominent in the small muscular arteries and arterioles, especially in the pia-arachnoid, basal ganglia, thalamus, mesencephalon, pons, and cerebellum. The most common changes are concentric thickening of the vascular wall and narrowing of the lumen by either subendothelial fibrous proliferation or smudgy hyaline degeneration of the intima, sometimes extending to the whole thickness of the wall. Reduplication and fragmentation of the internal elastic lamina is seen. Occasionally, fibrinoid necrosis, intramural edema, and an inflammatory infiltrate extending to the perivascular spaces are seen. These changes are strikingly similar to those reported in association with lipohyalinosis in cases of hypertensive subcortical ischemia. A possible distinguishing feature was elicited on histochemistry, which showed strong staining for periodic acid–Schiff (PAS) in the thickened intima in CADASIL that was unchanged by prior lipid extraction. Acetylation prevents the PAS positivity, indicating that the staining may be due to acid...
mucopolysaccharides (acid glycosaminoglycans). In three additional possible cases, staining with Alcian blue was positive. However, none of the histopathologic reports in cases of hypertension-associated subcortical ischemia state that staining for PAS was performed. In five cases of vascular dementia with small-vessel disease stained with Alcian blue at low pH, similar material was seen in the walls of the vessels (S. Gaytan, D. Munoz, V. Hachinski, unpublished data, 1994). Consequently, the absence of reports of PAS staining in hypertension-associated white-matter disease may be misleading. Whether this material is pathogenic or simply a consequence of some other process remains unsettled. Clarification will require, at the very least, identification of the material. Heparan sulfate in the cerebral vessel walls has been suggested.

Within the Japanese literature there is a second condition, possibly of autosomal recessive inheritance, in which cerebrovascular disease is a predominant finding, along with thin, aged-appearing skin. Intervertebral disk disease and spinal deformity at an early age may also be common features. Alopecia follows after the neurological presentation, which is similar to that described for CADASIL. The histopathology is also similar to that for CADASIL, although there is no mention of a PAS-positive eosinophilic deposit in the media of the affected vessels. These cases are clearly different from CADASIL and reflect a second genetic condition (CARASIL?) with a seemingly direct effect upon the cerebral vasculature.

While the PAS-positive material may prove not to be a hallmark of CADASIL, CADASIL appears to be a vascular disease and not one of the white matter. Given the young age of the patients with CADASIL, the even younger asymptomatic subjects who are MRI positive, and the detailed investigation in some series, it is clear that there are no other coexistent conditions. Ischemia must therefore be the basis of the white-matter changes. How do they arise? Some lesions are clearly infarcts attributable to occluded vessels, but what of the rest? Chronic ischemia does not occur in the deep white matter in hypoxic or hypoglycemia-associated subcortical ischemia, as the decreased blood flow is coupled with decreased metabolism. If such patients are given acetazolamide, a vasodilator, they do not exhibit the increase in regional cerebral blood flow seen in normal elderly individuals, which suggests that these patients have decreased perfusion reserve. To translate this into a pathophysiological mechanism for the white-matter changes, it has been postulated that these patients undergo episodic hypotension, causing ischemia in the zones of decreased perfusion reserve, and that the patterns of white-matter change seen could be caused by modest decreases in perfusion of this kind.

There is, however, no conclusive evidence. Limited to CADASIL, the question is important to a few individuals. However, leukoaraiosis, some of which may occur on the same hemodynamic basis as CADASIL, is increasingly being identified by MRI and may be treatable if a hemodynamic disturbance in addition to small-vessel disease can be shown to be the mechanism.

Two new genetic diseases affecting the small vessels of the brain, one autosomal dominant and one recessive, have recently been described. It will be of interest to see whether they shed any light on small-vessel cerebrovascular disease in general. In response to hypertension some, but importantly not all, individuals develop the pattern of a small-vessel disease termed lipohyalinosis. With this, white-matter changes occur that may in some be the basis of vascular cognitive impairment. We speculate that these individuals also have a genetic predisposition to small-vessel disease that manifests itself in the presence of other risk factors for vascular disease. This could be clarified by carrying out familial studies in cases in which neuroimaging has identified leukoaraiosis in relatively young subjects. Whether any such predisposition is directly related to CADASIL, perhaps as a different defect in the same gene, will require further study. The relationship between the PAS/Alcian blue staining material and small-vessel disease in cases of leukoaraiosis of all causes needs to be clarified. If the material is always associated with cerebrovascular disease, what is its origin? Is it pathogenic or merely a consequence of some other process? If the material is important, how is it related to the genetic abnormality?

The description and genetic identification of CADASIL represents a clinical and scientific triumph, combining the best of European classical neurology with the latest molecular technologies. The significance of the findings goes well beyond the condition itself. It paves the way for research into pathophysiology and encourages the search for related or less manifest disorders. It also represents an important step in elucidating the genetics of cerebrovascular disease, which are bound to play an increasingly important role. CADASIL represents a magnificent beginning.
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