Epidemiology of Ischemic Stroke

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INTRODUCTION

Ischemic stroke (IS) is a heterogeneous multifactorial disorder recognized by the sudden onset of neurologic signs related directly to the sites of injury in the brain where the morbidity process occurs. The evaluation of complex neurologic disorders, such as stroke, in which multiple genetic and epigenetic factors interact with environmental risk factors to increase the risk has been revolutionized by the genome-wide association studies (GWAS) approach. This approach has the potential to provide insight into appropriate individual and population risk reduction and public health policy approaches to avert irreversible sequela and burden of stroke.

The importance of addressing stroke through well-devised epidemiologic studies was underscored by the Global Burden of Disease 2013 Study (GBD 2013). The GBD 2013 used world mapping to visualize stroke burden and its trends in various regions and countries using epidemiologic measures of age-standardized incidence, mortality, prevalence, disability-adjusted life years, and years lived with disability associated with stroke from 1990 to 2013. Their findings showed that the absolute

KEYWORDS

Stroke • Public health • Epidemiology

KEY POINTS

• The burden of ischemic stroke is considerably impacting populations of every age group, ethnicity, race, and country.
• Genetic factors are important in the development of ischemic stroke that may be unique or differentially impact on individuals or populations.
• Large, well-powered genome-wide association study analyses have uncovered significant associations in ischemic stroke.
• The domestic and global burden of ischemic stroke makes it an important public health concern.

The authors have nothing to disclose.

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number of people affected by stroke substantially increased across all countries in spite of dramatic declines in age-standardized incidence, prevalence, mortality rates, and disability. Population growth and aging have played an important role in the observed increase in stroke. With significant geographic country and regional differences and developing countries sharing in the impact of stroke, the domestic and global burden of this disease may actually be borne by low- and middle-income populations making it a public health concern. This article addresses the epidemiologic approaches to stroke and its present domestic and global burden.

EPIDEMIOLOGY OF STROKE

Stroke is the leading cause of morbidity and mortality in industrialized countries. Residents of northern Manhattan have been the source of epidemiologic interest since 1998 when the Northern Manhattan Stroke Study (NOMASS) conducted a population-based study designed to determine stroke incidence, risk factors, and prognosis in the multiethnic urban population of northern Manhattan. Based on the 1990 census, the initial population of about 260,000 people were 40% older than 39 years, 20% black, 63% Hispanic, and 15% white. This community has been exhaustively studied for nearly 2 decades by investigators at the New York Presbyterian/Columbia Presbyterian Medical Center, the only hospital in the region. The later 2000 US census served as a model for race-ethnicity questionnaires in establishing baseline demographics of the northern Manhattan study cohort. The 2006 Take Care New York (TCNY) community health appraisal of northern Manhattan published by the New York City Department of Health and Mental Hygiene added useful socio-demographic information for this ethnically and racially diverse community that now comprises 71% Hispanics, 14% blacks, 11% whites, and 2% Asians or others. With nearly 1 in 10 Inwood and Washington Heights residents of northern Manhattan using the emergency department when sick or in need of health advice, and about a third lacking a regular health care provider, the health needs of the community have been adequately addressed by the consortium of New York Presbyterian/Columbia Presbyterian Medical Center satellite hospitals and clinics. According to TCNY there was a decrease in the annual mortality rate of 20% in the past decade mirroring that of New York City (NYC) overall. Between 2003 and 2004, the average annual mortality rate in Inwood and Washington Heights was 8% lower than in Manhattan and greater than 10% lower than NYC with respective annual mortality rates of 640, 697, and 718 per 100,000.

For almost 2 decades, NOMASS collaborators from the Departments of Neurology and public health at Columbia University, Miller School of Medicine, and the College of Global Public Health of New York University have evaluated risk factors related to IS. The initial study by Sacco and colleagues enrolled 924 northern Manhattan residents aged 20 years or more, of white, black, or Hispanic race and ethnicity with neurologic symptoms deemed due to stroke over a 4-year period from 1993 to 1997 and provided insight into racial and ethnic differences associated with stroke. A comparison of the incidences of subtype- and age-specific stroke rates stratified by sex, race, and ethnicity detected 2- to 3-fold differences in stroke incidence rates with blacks and Hispanics at greater stroke risk than white residing in the same urban community. Although overall stroke cases comprised mainly cerebral infarction (CI) in 77%, hemorrhagic stroke cases, including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), were encountered among blacks with a 1.4- and 2.1-fold greater risk, respectively. A weakness of the study was the exclusion of patients with milder stroke who were not hospitalized. Later studies by the same investigators noted
that in adults aged 20 to 44 years, only 45% of strokes were caused by CI, with 31% ICH and 24% SAH, compared with 80%, 14%, and 5%, respectively, in older individuals. A cryptogenic etiopathogenesis of stroke occurred more frequently in younger than older adults, 55% versus 42%; cardio-embolic stroke occurred less frequency: 6% versus 22% in young versus older. However, extracranial and intracranial atherosclerosis and lacunar infarction occurred with about equal frequency. Men had a case fatality rate of 21% compared with 11% for women. The relative risk of any stroke was greater in younger blacks and Hispanics than in whites, with an overall case fatality rate that was highest in ICH followed by SAH and infarct. NOMASS has investigated other risk factors associated with stroke in northern Manhattan using increasingly more sophisticated epidemiologic study designs and complex questions commensurate with the increasing body of knowledge associated with stroke morbidity and mortality.

Sacco and colleagues carried out a population-based case-control study between 1993 and 1997 examining alcohol consumption. They detected the beneficial protective effects of moderate alcohol consumption of up to 2 drinks per day for IS after adjustment for risk factors of cardiac disease, hypertension, diabetes mellitus (DM), current smoking, body mass index, and education in younger and older men and women and in whites, blacks, and Hispanics. A weakness of the study was the lack of distinction between consumption of red wine and white wine and a variety of biases with a possible trend toward alcohol use in the community. Elkind and colleagues provided additional insight into the role of moderate alcohol consumption noting that after adjusting for risk factors compared with those who did not drink in the past year, moderate drinkers had a reduced risk of IS (0.67; 95% confidence interval, 0.46–0.99). Their results were similar when never-drinkers were used as referent group. The salutary effect of moderate alcohol consumption was independent of other risk factors and held for nonatherosclerotic stroke subtypes.

Sacco and colleagues carried out a population-based incident case-control study of racial-ethnic disparities on the impact of stroke risk factors that revealed the association of hypertension (HTN) and DM in blacks and Hispanics and atrial fibrillation and coronary artery disease (CAD) in white northern Manhattan residents. A weakness of the study was the lack of insight into physical activity. Gardener and colleagues carried out a population-based prospective cohort study of Mediterranean style diet (MedDi) and risk of IS, myocardial infarction (MI), and vascular death demonstrating the inverse relation between MedDi score and composite outcome of IS, MI, or vascular death. A weakness of the study was the lack of relation to race-ethnicity despite MeDi in Hispanics. In a related study of dietary fat intake and IS risk more typical of a Western diet, stroke-free community residents of northern Manhattan more than 40 years of age underwent evaluation of their medical history and had their diet assessed by a food-frequency survey. Cox proportional hazard models calculated the risk of incident IS. During a mean of 5.5 years of follow-up, 142 IS occurred. After adjusting for potential confounders, the risk of IS was higher in the upper quintile of total fat intake compared with the lowest quintile. Total fat intake greater than 65 g was associated with increased risk of IS. Risk was attenuated after controlling for caloric intake. The results suggested that increased daily total fat intake, especially greater than 65 g, characteristic of a Western-type diet significantly increased the risk of IS.

The impact of an underlying metabolic syndrome recognized by the constellation of vascular risk factors, including elevated blood pressure, elevated blood glucose, obesity, and dyslipidemia, on IS was later investigated by Boden-Albala and colleagues in a prospective, population-based cohort study. Subjects aged 40 years
or older, never diagnosed with IR, and residing in northern Manhattan were found to have an increased risk of IS and vascular events after adjustment for sociodemographic and risk factors. The effect of the metabolic syndrome on IS risk was greater among women than among Hispanics compared with blacks and whites. An analysis of the etiologic fraction estimate suggested that elimination of the metabolic syndrome would result in a 19% reduction in overall stroke, a 30% reduction of stroke in women, and a 35% reduction of stroke among Hispanics.

The population-attributable risks of HTN and diabetes for IS was studied by Willey and coworkers using multivariable Cox models to calculate the hazard ratio (HR), population attributable risk (PAR), and 95% confidence intervals for the end point of stroke. The PARs resulting from HTN and diabetes were, respectively, 29.9% (95% confidence interval, 12.5–47.4) and 19.5% (95% confidence interval, 12.4–26.5) for stroke. The PAR resulting from HTN and diabetes for stroke differed by race-ethnicity and age (P for differences <.05). PAR for stroke resulting from HTN was greater among Hispanics (50.6%; 95% confidence interval, 29.2–71.9) than non-Hispanic whites (2.6%; 95% confidence interval, −33.2 to 38.6). The PAR for stroke resulting from HTN and diabetes was greater in those less than 80 years of age than in those 80 years of age and older. These results concluded that HTN and diabetes have important effects on the burden of stroke, particularly among those younger than 80 years and Hispanics.

There are guidelines for the primary prevention of IS. Important nonmodifiable risk factors for IS include age, sex, ethnicity, and heredity. Modifiable risk factors include HTN, cardiovascular disease (CVD), DM, hyperlipidemia, asymptomatic carotid stenosis, cigarette smoking, and alcohol abuse. Data from NOMASS also provided new insights into these stroke risk factors. Physical activity had a protective effect against stroke, with relatively low levels of exercise, such as regular walking, producing this effect. High-density lipoproteins (HDLs) were protective against stroke, whereas lipoproteins increased stroke risk. If stroke is subdivided into atherosclerotic, large-artery carotid disease, and intracranial atherosclerotic disease and nonatherosclerotic cryptogenic, lacunar, and cardio-embolic stroke categories, the protective effect of HDL was increased further in events of atherosclerotic origin. Drug treatment to lower low-density lipoprotein (LDL) and triglyceride levels and increase HDL reduces the risk for stroke as well as cardiovascular events.

There is evidence to suggest that blood vessel endothelial injury is involved in the atherosclerotic process and linked to increased incidence of stroke, mechanisms of which could include elevated homocysteine levels and infectious agents that infect the endothelium. Homocysteine, an important new risk factor for stroke, is both genetically and environmentally controlled. Some individuals with homocysteinemia have a genetic defect in the enzyme cystathionine β synthetase. One-half of affected patients who are homozygous for the enzyme defect die at a young age of venous thrombosis and premature atherosclerosis, whereas heterozygous individuals are at risk for premature atherosclerosis. Chlamydophila pneumoniae, a common cause of community-acquired pneumonia, pharyngitis, and sinusitis and bacterial flora involved in periodontal disease, is theoretically capable of infecting the endothelium and inflicting injury and may provide useful predictors of IS. The sum total of these injurious events of the endothelium could stimulate platelet aggregation, adhesion, monocyte migration, and plaque formation, so as to begin the atherosclerotic process, increasing the risk of stroke. Periodontal disease, which affects up to 20% of those aged 60 years to 64 years, can be an important infectious agent and could theoretically elevate C-reactive protein levels, increasing the risk of CVD and stroke.
The Greater Cincinnati/Northern Kentucky Stroke Study estimated that 37% to 42% of all IS in blacks and whites could be attributable to the effects of DM alone or in combination with HTN; however, those with IS and DM tended to be younger and black, with HTN, MI, and higher cholesterol levels than non-DM. Early population-based epidemiologic studies in elderly individuals revealed an association of carotid artery atherosclerosis with stroke risk with the assumption that increasing age, HTN, systolic blood pressure, DM, and smoking but not lipids and lipoproteins were consistently related. Data on elderly patients studied by NOMASS demonstrated that apolipoprotein A-1 and B were significant determinants of moderate to severe carotid artery atherosclerosis; HLD was protective, whereas total cholesterol, triglycerides, and LDL cholesterol showed no association.

Although a single most likely cause of CI is emphasized in leading stroke registries, other investigators have emphasized the multiple potential causes of infarct. The Lausanne, Belsancon, and Ege Stroke Registries noted rates of multiple potential causes of CI of 7.0%, 4.7%, and 3.4%, respectively. This phenomenon has probably been underestimated in the literature, because several other stroke registries have sometimes included patients with 2 potential causes of infarct in “undetermined” subgroups. In ascertaining the frequency of multiple potential causes of CI, the Lausanne Stroke Registry distinguished subgroups of patients with large and small-artery disease and cardiac embolism as follows: Large-artery disease was diagnosed in those with 1 or more risk factors, including age greater than 50 years, arterial HTN, DM, cigarette smoking, hypercholesterolemia, stenosis of at least 50% of the lumen diameter in the appropriate large artery demonstrated by Doppler ultrasonography, 3-dimensional magnetic resonance imaging (MRA), and conventional cerebral angiography. Small-artery disease was presumed in those with long-standing arterial HTN or DM and a CI less than 15 mm in diameter limited to the territory of deep perforating vessels, in the absence of a cardiac or arterial source of embolism. Cardiac embolism was presumed in the presence of endocarditis, mitral stenosis, atrial fibrillation, sick sinus syndrome, intracardiac thrombus or tumor, prosthetic aortic or mitral values, left ventricular aneurysm or akinesia after MI, and global cardiac hypokinesia or dyskinesia. One particular type, pure motor stroke, so noted in 52% of patients, was the most common lacunar syndrome in the Lausanne Stroke Registry followed by ataxic hemiparesis in 13% and dysarthria-clumsy hand syndrome in 3%. Pure motor stroke in 71% predominated in the patients with both large-artery and cardiac embolic disease, as did ataxic hemiparesis and pure motor stroke, which occurred in one-third each of patients with combined large and small-artery disease and cardiac embolism.

NEURORADIOLOGIC METHODS TO DETECT STROKE

It is noteworthy to describe the available methods to detect stroke used in routine care and clinical studies. Brain computed tomography (CT) and MRI using T1- and T2-weighted equally sensitive to the detection of ischemic stroke and hematoma. The addition of diffusion-weighted imaging (DWI) to the latter, detects ischemic regions within minutes of symptom onset, as well as, relatively small cortical and subcortical lesions including those in the brainstem and cerebellum, and other valuable information about the vascular territory with a sensitivity and specificity that approaches 100%. Additional available studies for stroke evaluation, including 3-dimensional MRA of arteries of the neck and cerebral circulation, extracranial and transcranial Doppler ultrasonography with frequency spectral analysis, and B-mode echo tomography of the carotid, vertebrobasilar, and selected intracranial arteries, are all readily available.
available at most centers and can provide useful information in stroke classification and management.

Acute IS occurs when a cerebral vessel is occluded and a core of brain tissue dies; however, the surrounding area termed the ischemic penumbra, which is hypoperfused, remains at risk of further infarction. Deep brain ischemic leads to a cascade of Na⁺/K⁺ channels that results in cytotoxic edema with the net uptake of water in affected brain tissue and narrowing of the extracellular matrix due to reduction in Brownian molecular motion. The categorization of subtypes of IS is more than an academic exercise because it is inextricably linked to further management, the goal of which is to accurately ascertain the site, size, age, and vascular territory of an ischemic lesion within hours of symptom onset by early brain neuroimaging and to consider one of the many treatment protocols, including intravenous recombinant tissue plasminogen activator (rt-PA), and other measures to restore or improve perfusion, without which the infarcted core may continue to enlarge and progressively replace ischemic tissue in the penumbra.

The categorization of subtypes of IS, previously based on risk factor profiles, clinical features of the stroke, and findings on brain imaging using CT and MRI, has shifted in the direction of etiopathogenesis recognizing the 5 essential types for purposes of acute management in clinical trials, including large-artery atherosclerotic embolic and thrombotic, moderate- and high-risk cardioembolic, small-vessel occlusive lacunar, and those due to other causes, undetermined, or with negative or incomplete evaluations. Although noncontrast CT of the brain has been the standard for evaluation of patients with suspected stroke and to which all other brain imaging studies are compared, it is insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. With the advent of rt-PA treatment there has been interest in refining CT to identify subtle early signs of ischemic brain injury and arterial occlusion that might impact on the decision to treat with rt-PA based on the more favorable outcome of the ischemic penumbra administered within 3 hours of symptom onset. Such refinements in CT imaging include perfusion-CT using whole-brain perfusion and dynamic perfusion that allow differentiation of reversible and irreversible ischemia and identification of the ischemic penumbra and helical CT angiography to rapidly and noninvasively evaluate vascular stenosis and occlusions, all with the benefit of rapid data acquisition and performance with conventional CT equipment but the disadvantage of the requirement for iodine contrast and additional radiation exposures. The combination of perfusion-weighted imaging (PWI) to demonstrate areas of reduced cerebral perfusion along with DWI to depict areas of irreversible injury leads to mismatched areas, the PWI often being larger than DWI, representing the tissue at risk in the ischemic penumbra. Prospective studies of patients studied with sequential neuroimaging for ACI that included DWI, PWI, T2-weighted MRI and MRA, 35 patients subjected to rt-PA with mismatch of PWI/DWI in the area of ischemic penumbra, and cerebral arterial occlusion shown by MRA showed significant reduction in infarct size and recanalization consistent with salvation of at-risk ischemic tissue.

GENETIC BASIS OF STROKE

IS is considered to be a highly complex disease consisting of a group of heterogeneous disorders with multiple genetic and environmental risk factors and can, therefore, be viewed as a paradigm for late-onset, complex polygenic diseases. Several lines of evidence support a role for genetic factors in the pathogenesis of stroke, including studies of twins and familial aggregation. Both environmental
and genetic risk factors for IS have been well characterized. Duggirala and co-workers demonstrated high heritability, with 66.0% to 74.9% of the total variation being accounted for by genetic factors and the remainder being attributable to covariates, such as lipids, diabetes, HTN, and smoking. Catto and colleagues reviewed evidence that stroke had a genetic basis and that the hemostatic system was an important risk factor.

The association between the stroke and a specific allele of a single nucleotide polymorphism (SNP) within functional candidate genes has been analyzed between patients and controls. Most such studies however use relatively small numbers of patients and controls, and their results may not be replicated. A disadvantage of the hypothesis-based approach to candidate gene studies is that the genes involved in the pathogenesis of the disease, such as stroke, through unknown pathways may be overlooked. The hypothesis-free approach used by GWAS allows stroke research to overcome this drawback because in these studies nearly all common variants in the entire genome can be tested for their associations. There is a catalogue of published GWAS available online (http://www.genome.gov/26525384). In contrast to linkage studies, GWAS use readily available case-control data sets rather than multiplex family based sets, permitting collection of much larger data sets. Early stroke studies that used GWAS examined the association with CVD. Two loci on chromosome 4q25 in PITX2 and at 16q22 in ZFHX3 associated with atrial fibrillation were found to be risk factors for cardioembolic stroke similar to another on chromosome 9p21 originally associated with CAD and later found to be a risk factor for large-artery stroke. It is now recognized that different genetic risk factors predispose to specific stroke subtypes. For example, the variant in the protein kinase C family of PRKCH associates with small-vessel stroke, whereas variants associated with PITX2 and ZFHX3 predict cardioembolic stroke, while those associated with HDAC9 and the 9p21 loci predispose to large-vessel stroke.

Three loci, respectively, at 1q24.2 in Factor V (F5) encoding coagulation factor V, at 7q36.1 in nitric oxide synthase 3 encoding human endothelial nitric oxide synthase, and at 11p11.2 in Factor II encoding a 622-residue prepropeptide with a molecular mass of about 70 kD, are all associated with IS susceptibility; one at 13q12.3 in arachidonate 5-lipoxygenase activating protein (ALOX5AP) encoding 5-lipoxygenase-activating proteins associated with stroke susceptibility and another at 14q23.1 in PRKCH (protein kinase C) encoding PRKCH that is associated with susceptibility to CI.

Bersano and colleagues reviewed genetic polymorphisms implicated in the development of stroke. Candidate genes included those involved in hemostasis (F5), the renin-angiotensin-aldosterone system (angiotensin-converting enzyme), homocysteine (methylenetetrahydrofolate reductase), and lipoprotein metabolism (apolipoprotein E). Campbell and colleagues noted that increased serum levels of soluble vascular adhesion molecule-1 (vascular cell adhesion molecule 1) predicted recurrent IS in a study of 252 patients. A smaller but similar trend was noted for serum levels of N-terminal pro-B-type natriuretic peptide (natriuretic peptide precursor B).

In a GWAS of 4 large cohorts, including 19,602 Caucasians in whom 1544 incident strokes developed over an average follow-up of 11 years, Ikram and coworkers found linkage to rs11833579 and rs12425791 on chromosome 12p13 near or within the NINJ2 gene. Both SNPs showed significant associations with total stroke (P = 4.8 x 10^-9 and P = 1.5 x 10^-8, respectively) and IS (P = 2.3 x 10^-10 and P = 2.6 x 10^-9, respectively). A significant association with rs12425791 was replicated in 3 additional cohorts, yielding an overall HR of 1.29 (P = 1.1 x 10^-9). The International Stroke Genetics Consortium and Wellcome Trust Case-Control Consortium were unable to replicate an association between IS and the rs11833579 and
rs12425791 variants at 12p13 in a combined sample of 8637 cases and 8733 controls of European ancestry as well as in a population-based genome-wide cohort study of 278 IS among 22,054 participants.

GENETIC ANIMAL MODEL

Rubattu and colleagues\(^5\) studied the stroke-prone spontaneously hypertensive rat as a model organism for a complex form of human stroke, mating it with the stroke-resistant spontaneously hypertensive rat. The investigators then performed a genome-wide screen in the resultant cohort whereby latency until stroke but not HTN (a major confounder) segregated identifying 3 major quantitative trait loci, STR1-3, with lod scores of 7.4, 4.7, and 3.0, respectively, that accounted for 28% of the overall phenotypic variance. STR2 colocalized with the genes encoding atrial and brain natriuretic factor peptides with important vasoactive properties.

GENETICS OF STROKE IN YOUNG ADULTS

Terni and colleagues\(^5\) reviewed the single-gene causes of IS in young adults noting that IS was a common cause of admission of young patients in stroke units. In particular, the yearly incidence of stroke increased from 2.4 per 100,000 in people aged 20 to 24 years, to 4.5 per 100,000 for those aged 30 to 34 years, and to 32.9 per 100,000 for people aged 45 to 49 years. Stroke was slightly more frequent in women aged 20 to 30 years and in men older than 35 years. Traditional risk factors for stroke, such HTN and DM, and large extracranial and intracranial atherosclerosis, small-vessel disease, and atrial fibrillation, which play an important role in older patients, occur less frequently in young adults. The main clinical challenge in management of a young adult with stroke is the identification of its cause, which may remain undetermined. Four monogenic disorders can manifest stroke as a prominent finding.

Mitochondrial encephalomyopathy with lactic acidosis and strokelike episode is a maternally inherited mitochondrial disease. Point mutations occur in polypeptide-encoding and transfer RNA (tRNA) genes, notably, A3243G and T3271C in tRNA Leu (UUR).\(^5\) Familial hemiplegic migraine leads to strokelike episodes in childhood and teenage years with heterozygous mutations in the calcium ion channel gene (CACNA1A) at chromosome 19p13.13 encoding the alpha 1 subunit of the voltage-gated calcium channel in neurons.

Cerebral autosomal dominant (AD) arteriopathy with subcortical infarcts and leukoencephalopathy type 1 due to AD mutations in the NOTCH3 gene on chromosome 19p13.12 is a progressive disorder of the small arterial vessels of the brain manifested by migraine, strokes, and white matter lesions, with resultant cognitive impairment in some patients.\(^5\)

Cerebral small-vessel disease can be associated with mutations in the collagen type IV gene (COL4A1) at chromosome 13q34 encoding the \(\alpha 1\) subunit of collagen type IV is an AD disorder that presents IS and to a lesser extent ICH with or without ocular anomalies. Shah and colleagues\(^5\) described 5 affected children from 4 families with recurrent stroke, infantile hemiplegia/spastic quadriplegia, infantile spasms, and ocular anomalies identifying heterozygosity for 4 different missense mutations in the COL4A1 gene, including the G755R substitution in 1 boy and a G773R substitution (120130.0021) in 2 sibs.

Fabry disease is an X-linked congenital lysosomal storage disorder due to a mutation in the GLA gene encoding alpha-galactosidase A on chromosome Xq22. The disorder is a systemic disease, manifest as progressive renal failure and cardiac disease with IS, small-fiber peripheral neuropathy, and skin lesions, among other abnormalities.\(^5\)
GENETIC INFLUENCES OF WHITE MATTER LESION AND HYPERINTENSITY PROGRESSION

White matter hyperintensities (WMHs) or white matter lesions (WMLs) on T2-weighted MRI are associated with increasing age and cardiovascular risk factors, particularly HTN, and are predictive of both stroke and dementia in prospective community populations. Severe confluent WMHs are often found in patients presenting with stroke and are more common in patients with the small-vessel stroke subtype. The WMH burden is linked to poor clinical outcomes after stroke, making it important to understand the possible heritable aspects.

Hofer and colleagues estimated heritability of WML progression and sought common genetic variants associated with WML progression in elderly participants from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. To assess the relative contribution of genetic factors to progression of WML, the investigators used cohort risk models that included demographics, vascular risk factors, plus SNPs that were known to be associated cross-sectionally with WMLs. Among 1085 subjects that showed WML progression, the heritability estimate for WML progression was 6.5%, and no SNPs achieved genome-wide significance ($P < 5 \times 10^{-8}$). SNP variants were previously related to WML explained only 0.8% to 11.7% more of the variance in WML progression than age, vascular risk factors, and baseline WML burden. Thus, common genetic factors contribute little to the progression of age-related WMLs in middle-aged and older adults. Although the contribution of genetic factors seems to be large during the initiating phase of white matter damage, the propagating phase of WMLs seems to be mainly influenced by nongenetic determinants. With the exception of HTN, these nongenetic risk factors for WML progression remain largely unknown.

Verhaaren and colleagues conducted a meta-analysis of multiethnic GWAS influencing WMH burden among 21,079 middle-aged to elderly individuals from 29 population-based cohorts free of dementia and stroke and of European, African, Hispanic, or Asian descent. Four novel genetic loci that implicated inflammatory and glial proliferative pathways in the development of WMH were identified. A meta-analysis conducted for each ethnicity separately and for the combined sample confirmed a previously known locus on chromosome 17q25 ($P = 2.7 \times 10^{-19}$) and identified novel loci on chromosome 10q24 ($P = 1.6 \times 10^{-9}$) and 2p21 ($P = 4.4 \times 10^{-8}$) in those of European ancestry and 2 additional loci on chromosome 1q22 ($P = 2.0 \times 10^{-8}$) and 2p16 ($P = 1.5 \times 10^{-8}$) in multiethnic ancestry.

Traylor and colleagues conducted GWAS of WMH volumes (WMHV) for 3670 patients with stroke from the United Kingdom, United States, Australia, Belgium, and Italy. Genetics associations were sought with WMHs in a stroke population and then examined as to whether genetic loci previously linked to WMHV in community populations also associated in patients with stroke. Having established that genetic associations were shared between the 2 populations, meta-analysis testing was performed. There were no associations at genome-wide significance with WMHV in patients with stroke concluding that genetic associations with WMHV are shared in otherwise healthy individuals and patients with stroke indicating a common genetic susceptibility in cerebral small-vessel disease.

GENETIC ASPECTS OF LACUNAR STROKES

Traylor and colleagues studied the genetic aspects of lacunar strokes noting that they composed about 20% of all strokes, yet GWAS had not been informative. Pathologic and radiological studies suggested that there may be different pathologies underlying lacunar strokes leading to the differentiation into isolated lacunar infarcts and...
multiple lacunar infarcts and leukoaraiosis. The investigators performed GWAS in MRI-verified cohort of 1012 lacunar stroke cases and 964 controls. By the extent of leukoaraiosis grade, patients were subtyped into 2 groups: isolated lacunar infarct and single lacunar infarct with absent or mild leukoaraiosis or lacunar infarct with moderate or severe confluent leukoaraiosis. An assessment of heritability of lacunar stroke was performed using a calculation of genetic relationships across 8,122,203 SNPs after discarding genotypes and SNPs with a probability less than 90%. Their results indicated a substantial heritable component to MRI-verified lacunar stroke in 20% to 25% and its 2 subtypes: isolated lacunar infarct in 15% to 18% and multiple lacunar infarcts/leukoaraiosis in 23% to 28%. This heritable component was significantly enriched for sites affecting expression of genes. The risk of the 2 subtypes of lacunar stroke in isolation, but not in combination, was associated with rare variation in the genome. Because the investigators partitioned their choice of SNP data on regulatory regions, including all SNPs that overlapped a transcription factor–binding site and DNase peak, as well as either having a matched transcription factor motif or a matched DNase footprint, the SNPs represented regions where regulatory factors were thought to bind to the genome.

GENETIC BASIS FOR STROKE AND MIGRAINE

Migraine is a headache disorder characterized by recurrent attacks of severe, often throbbing, headache. Most patients have migraine without aura (MO); however, a third have headaches preceded by aura (MA) composed of transient neurologic disturbances. Epidemiologic studies have shown a doubling of the risk of IS in people who have MA, and one large meta-analysis of case-control and observational cohort studies reported that the risk of stroke is increased in people with migraine (relative risk [RR] 2.16, 95% confidence interval 1.89–2.48). This increase in risk was consistent in people who had MA (RR 2.27, 1.61–3.19) and MO (RR 1.83, 1.06–3.15) as well as in those taking oral contraceptives (RR 8.72, 5.05–15.05). A meta-analysis of 9 studies that investigated the association between any migraine and IS revealed a significantly higher risk among people who had MA (RR 2.16, 1.53–3.03) compared with people who had MO (RR 1.23, 0.90–1.69; meta-regression for aura status \( P = .02 \)). Although the pathophysiology linking IS and MA or MO is poorly understood, suggested mechanisms include cortical spreading depression, endothelial dysfunction, enhanced platelet activation, and vasoconstriction. Malik and colleagues investigated the shared genetic basis of migraine and IS noting shared genetic susceptibility to migraine and IS, with a particularly strong overlap between MO and large-artery IS.

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