Nontraditional Risk Factors for Ischemic Stroke
An Update
Oh Young Bang, MD; Bruce Ovbiagele, MD; Jong S. Kim, MD

Although it is encouraging that during the past decade there has been a notable decline in the incidence of stroke in several countries around the world, further reductions in stroke occurrence will require even better treatment of conventional risk factors, as well as the identification and treatment of nontraditional risk factors. Hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, atrial fibrillation, and carotid stenosis are definite causal risk factors because randomized controlled trials showed that treating them reduced the incidence of ischemic stroke/transient ischemic attack (TIA) or because epidemiological studies have shown that they are prospectively and independently associated with incident risk of stroke. Several risk models and risk calculators are available for stroke. However, they include only a few traditional risk factors, and not all ischemic strokes are explained by these factors. About 60% to 80% of all ischemic strokes can be attributed to these factors. Adding more factors may improve the predictive values of the risk models for stroke, and controlling nontraditional risk factors may further reduce stroke risks. The INTERSTROKE study, which examined 10 factors including less traditional factors such as obesity, psychosocial stress and depression, and ratio of apolipoprotein B to A1, found that these conditions were linked to 90% of the risk of stroke.

The carotid substudy of Northern Manhattan studies showed that traditional risk factors explain only a minority of the variability in carotid plaque, suggesting a possible role for unaccounted nontraditional risk factors in the development of atherosclerotic plaque. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study confirmed the existence of a stroke belt in the southeastern United States, where the rates of stroke mortality were higher (>40%) than those of other regions. However, in this study, only modest differences were found in 9 known risk factors common to stroke screening (the Framingham Stroke Risk Score) between the stroke belt and the stroke buckle compared with the rest of the United States. Similarly, a stroke belt with high stroke incidence was found in north and west China. Of note, a high prevalence of obesity was reported in stroke belts of both United States and China (Figure). These findings indirectly suggest a role for nontraditional risk factors to predict and prevent stroke.

Search Strategy and Selection Criteria
In this review, we defined traditional risk factors as those used in the Framingham study (ie, age, sex, hypertension, diabetes mellitus, cigarette smoking, cardiovascular disease [CVD], atrial fibrillation, and left ventricular hypertrophy) and hypercholesterolemia. Others are defined as nontraditional risk factors if the association between the factors and the occurrence of stroke was demonstrated with plausible biological explanation. We identified references for this review by searching PubMed and ClinicalTrials.gov published in English up to January 2015, with the search terms stroke, cerebral infarction, cerebrovascular, risk factor, and trigger. Additionally, we searched references from relevant articles and reviews. The final reference list was generated on the basis of originality and relevance to this topic. Because of space limitation, we were not able to discuss many nontraditional risk factors in depth with critical analysis. We did not include serological biomarkers such as homocysteine. Genetic studies are mentioned only briefly at the end because they are not modifiable risk factors.

Nontraditional Risk Factors
Identification of nontraditional risk factors for stroke is increasing. These conditions include obesity and metabolic syndrome, sleep apnea, chronic inflammation, chronic kidney disease (CKD), and nutrition/diet. In addition, exposure to certain conditions including psychosocial stress, environmental factors, infection, and alcohol abuse may exert a single, sharp, and transient effect on the pathophysiological process, precipitating the onset of stroke/TIA. However, it is often difficult to distinguish an emerging risk factor from a novel triggering factor, but nature (eg, abruptness) of exposure to the condition in temporal relation to occurrence of the stroke event and the severity of the condition may help in making this distinction.
Obesity and Metabolic Syndrome

During the past several decades, a striking rise in the number of people with the metabolic syndrome has taken place, associated with the global epidemics of obesity and diabetes mellitus. Most studies show an association of obesity with increased risk of stroke; for every 1-U increase in body mass index, the risk for ischemic stroke increases ≈5%, and the risk is nearly linear starting with a still normal body mass index of 20 kg/m².16–18 Weight reduction in overweight or obese individuals may reduce stroke risk because of favorable effects on blood pressure, cholesterol, and glycemic control. A recent large pooled analysis showed that about three quarters of the excess risk of stroke with high body mass index is mediated by combination of these traditional risk factors, which can be the target of intervention in addition to maintenance of optimum body weight.19 However, there is a paucity of high-quality data on effect of weight loss interventions on risk of vascular events. The Action for Health in Diabetes (Look AHEAD) study is the only randomized trial adequately designed to assess the role of a behavioral intervention for weight loss on vascular event risk.20 However, the modest weight loss achieved in Look AHEAD (ie, 6% of initial body weight) did not reduce risk for vascular events, and at this time, it can only be assumed that more substantial weight loss may have a significant effect on risk of vascular events. Indeed, results of a large nonrandomized, controlled cohort study of bariatric surgery reported a reduction in the incidence of stroke (adjusted hazard ratio, 0.66; 95% confidence interval, 0.49–0.90).21

Metabolic syndrome is a cluster of cardiovascular risk factors and metabolic alterations associated with excess fat weight. Lipid accumulation in the nonadipose tissue decreases hepatic and intramuscular insulin sensitivity,22 and higher plasma levels of adipokines (hormones secreted from adipose tissue) were associated with increased risks of ischemic stroke.23 In addition, perivascular adipose tissue surrounds coronary arteries, secretes proinflammatory cytokines, and may be involved in local stimulation of atherosclerotic plaque formation.24,25 The Insulin Resistance Intervention After Stroke (IRIS) trial will determine whether treatment of insulin-sensitizing drugs (eg, pioglitazone) improves cardiovascular outcomes of nondiabetic, insulin-resistant patients with stroke/TIA.26

Sleep-Disturbing Breathing and Obstructive Sleep Apnea

Recent studies have suggested that poor quality of sleep and daytime sleepiness may be linked to vascular events.27 Patients with stroke/TIA have a high prevalence of obstructive sleep apnea (OSA; 50%–70%).28 OSA may be under-recognized in patients stroke; 1 study showed that most patients did not have typical clinical features of OSA, such as obesity and

Figure. Distribution of stroke belt (top) and overweight/obesity (bottom) in United States and China. Modified from US Centers for Disease Control and Prevention (Death 35+, 2000–2006). BMI indicates body mass index. Reprinted from Xu et al13 and Gao et al14 with permission of the publisher. Copyright © 2013, the American Heart Association, Inc. Copyright © 2008, Oxford University Press.
daytime sleepiness.\textsuperscript{29} Polysomnography is recommended in acute stroke patients with high risk for OSA.\textsuperscript{30} A recent polysomnography study of patients with stroke showed that endothelial dysfunction and arterial stiffness correlated with sleep-disturbing breathing,\textsuperscript{31} suggesting that sleep-disturbing breathing may be an aggravating factor for vascular injury rather than due effects of a stroke. The association between sleep-disturbing breathing and ischemic stroke could be mediated through traditional risk factors, such as hypertension, diabetes mellitus, and atrial fibrillation. In addition to physical exercise, continuous positive airway pressure is preferentially recommended to stroke/TIA patients with moderate to severe OSA, daytime symptoms, and high cardiovascular risk profile.\textsuperscript{32,33} Several ongoing controlled trials are aiming to reduce cardiovascular risk or improve symptoms with continuous positive airway pressure (clinical trial identifier NCT01812993, NCT02029183, and NCT01097967). Besides OSA, nonapnea sleep disorders may also be associated with increased stroke risks. Nationwide population-based studies of Taiwan showed that insomnia predisposed individuals to increased risk of stroke, especially among young adults.\textsuperscript{32,33}

**Chronic Inflammatory Disease**

Chronic inflammation, such as is seen in patients with rheumatoid arthritis, has been shown to be a crucial factor in the development and progression of atherosclerosis. Although rheumatoid arthritis is an organ (ie, synovium)-specific inflammation, proinflammatory cytokines are released into the systemic circulation, resulting oxidative stress, insulin resistance, and endothelial dysfunction.\textsuperscript{34} Effective suppression of inflammation by antiinflammatory drugs (including methotrexate and tumor necrosis factor-\(\alpha\) blocking agents) may reduce the risk of CVD events.\textsuperscript{35} A recent study of a large primary care database (UK Clinical Practice Research Datalink), including participants with psoriasis and related disorders, bullous skin disorders, ulcerative colitis, Crohn disease, inflammatory arthritis, systemic autoimmune diseases, and systemic vasculitis, showed an increased risk of CVD with chronic inflammatory disease, calling for the importance of clinical management of such conditions to reduce cardiovascular risk.\textsuperscript{35} Chronic inflammation may also be involved in the development of atherosclerosis in persons without rheumatologic disorders. In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial of apparently healthy persons without hyperlipidemia but with elevated C-reactive protein levels (a marker of inflammation), rosuvastatin significantly reduced the incidence of major cardiovascular events including stroke.\textsuperscript{36} Furthermore, recent genetic and epidemiological data documented shared pathologies of chronic inflammatory diseases and atherosclerosis, and there have been attempts to use anti-inflammatory regimens for intractable atherosclerosis.\textsuperscript{37} The cardiovascular inflammation reduction trial (CIRT) is ongoing, evaluating the effect of very low dose of methotrexate in patients with stable coronary artery disease.

**Chronic Kidney Disease**

CKD has now been established as conferring higher risk for stroke and is strongly associated with cerebral small vessel diseases and cognitive impairment because the kidney and brain share unique susceptibilities to vascular injury, likely because of similar anatomic and functional features of small artery diseases.\textsuperscript{38} A meta-analysis showed that a baseline estimated glomerular filtration rate of \(<60\) mL/min per 1.73 m\(^2\) was independently related to incident stroke across a variety of participants and study designs.\textsuperscript{39} Averting future vascular events in patients with a low estimated glomerular filtration rate should be a primary goal\textsuperscript{40} because most patients with an estimated glomerular filtration rate \(<60\) mL/min per 1.73 m\(^2\) die of cardiovascular causes and not progression to end-stage renal disease.\textsuperscript{41} CKD is a strong independent predictor of mortality and poor outcome in patients with acute stroke.\textsuperscript{42} The prevalence of traditional cardiovascular risk factors is high in patients with CKD.\textsuperscript{43} In addition, oxidative stress, inflammation, and metabolic derangement were reported to be renal dysfunction–related factors for CVD, and endothelial dysfunction may be the key factors that might contribute to CVD.\textsuperscript{44} The Chronic Renal Insufficiency Cohort (CRIC) study recently showed that lifestyle factors, such as nonsmoking, overweight (body mass index, 25–30 kg/m\(^2\)), and regular physical activity, were associated with reduced risk of CKD progression and also reduced risk of atherosclerotic events.\textsuperscript{45} An American Heart Association Advisory recommended that healthcare providers should evaluate their vascular disease patients for the presence of CKD as a part of preventive care and treatment strategies.\textsuperscript{40}

**Diet and Nutrition**

Both poor nutrition and overnutrition predispose individuals to stroke. Although dietary supplementation with vitamins (eg, antioxidant vitamin, vitamin D, and folic acid), calcium, and \(\omega-3\) fatty acid does not reduce the risk of stroke, many foods and beverages affect the risk of stroke.\textsuperscript{46} These results suggest that beneficial effect of food (eg, fish)\(^\circ\) intake on stroke risk is likely to be mediated through interplay of a wide range of nutrients rather than 1 single component in food (eg, long-chain \(\omega-3\) fatty acid).\textsuperscript{47} An observational study (the REGARDS study), a clinical trial (the PREDIMED [Prevention With Mediterranean Diet] study), and a meta-analysis showed that high adherence to Mediterranean diet (high consumption of fruit, vegetables, nuts, whole grains, and olive oil; moderate consumption of fish; and low consumption of red meat) was associated with a lower risk of ischemic stroke.\textsuperscript{48-50} Other dietary patterns, including traditional Japanese diets, were associated with reduced risk of ischemic stroke but remain to be settled. Low intake of fat and animal protein may be associated with increased risk of hemorrhagic stroke, which is prevalent in Asian countries.\textsuperscript{51} In addition, there is growing evidence of the role of potassium intake in pathophysiology of stroke (eg, lowering blood pressure),\textsuperscript{52,53} calling for the need of randomized trials (dietary intake or supplementation) for prevention of stroke and its complications.

**Psychosocial Stress**

Psychosocial stress may trigger ischemic stroke/TIA, and the population-attributable risk is 4.7%.\textsuperscript{5} Population-based cohort studies of middle-aged and older adults (Multi-Ethnic Study of Atherosclerosis) and older adults (Chicago Health and Aging Project) showed that higher levels of psychosocial stress are associated with increased risk of stroke, which was not explained by known traditional risk factors.\textsuperscript{54,55} Various types of psychosocial stress, such as anxiety, hostility, and job
strain, have been related to increased risk of stroke or to triggering strokes, either by way of cumulative effects of repeated emotional experiences or because of an extreme acute emotional episode.56–57 Besides personal psychosocial stress, social stress may also be associated with sudden surges of acute stroke. In the areas highly flooded by the tsunami caused by the Great East Japan earthquake (2011), the occurrence of cerebral infarction among elderly men more than doubled in the first 4 weeks after the disaster, and then declined to the same level as before the disaster.58

**Depression, Fatigue, and A-Type Behavior**

Depression was reported to be an independent risk factor of stroke.59 However, there have been arguments that depression may be associated with medical comorbidities or subclinical previous brain ischemic changes rather than be directly causing strokes. Nevertheless, 2 recent meta-analysis of prospective studies showed that depressed symptoms at baseline are associated with subsequent risk of stroke.60–61 Depression may produce strokes by way of inducing neuroendocrine dysregulation, heart rate variability, platelet aggregation, systemic inflammation, poor health lifestyle, and reduced medical compliance.62–65 It could be associated with the use of antidepressants.66 Although less convincing than depression, anxiety, phobic attacks67,68 or extreme fatigue/vital exhaustion69,70 is reported to be related with occurrence of future stroke. Type A behavior, characterized by aggressiveness, ambition, competitiveness, time urgency, and impatience, has been associated with increased risk of stroke in several studies71,72 but not in other.73 Perhaps, only certain components of type A behaviors may be related to a specific type of stroke; for example, tension score was related with atherosclerotic type of stroke.74 Type A behaviors are related with increased catecholamine secretion and hypothalamic–pituitary axis activity against stress, which may result in rigidity/atherosclerosis in cerebral arteries.74

**Air Pollution**

There is accumulating evidence of a relationship between air pollution and ischemic stroke risk.75–77 One study measured the air pollution (ie, level of fine particulate matter <2.5 μm in diameter) in Boston and showed that particulate matter <2.5 μm in diameter exposure increase the risk of ischemic stroke at levels below those currently considered safe under US regulations.78 Particulate matter may potentiate risk factors, and patients with pre-existing illness, such as traditional risk factors, subclinical atherosclerosis, or prior stroke, were susceptible to air pollution–associated stroke risk.77 The association between air pollution and ischemic stroke risk could be mediated through direct and indirect effects of exposure to air pollutants on heart rate modulation,79 arrhythmia,80–82 plasma viscosity,83 systemic inflammation,84 and endothelial dysfunction.85 In addition, increase of ischemic stroke admission and mortality in East Asian could be at least, in part, explained by the Asian dust (yellow sand).86–88

**Infection**

Certain infectious agents, such as *Chlamydia pneumonia*, *Helicobacter pylori*, and cytomegalovirus, are capable of invading the endothelium and have been implicated in cervicocephalic atherosclerotic process.92–94 In addition, recent infections (respiratory infection and bacteremia) were associated with atherosclerotic stroke or coronary disease, suggesting a triggering role of infectious agent in stroke.95,96 Periodontal disease, one of the most common infections, was found to be an important risk factor for ischemic stroke.97,98 These findings raise the possibility of remediation because infectious diseases are treatable. Interestingly, maintaining periodontal health by receiving dental prophylaxis and periodontal disease treatment reduced the incidence of ischemic stroke.99 However, a recent randomized controlled trial of preventive antibiotics showed negative results.100 Finally, several viral diseases have recently emerged and impacted healthcare system worldwide, such as Ebola virus disease, severe acute respiratory syndrome, and recently Middle East respiratory syndrome coronavirus. Acute thrombotic events, including deep venous thrombosis/pulmonary embolism and large artery ischemic stroke, were described in severe acute respiratory syndrome patients, which may related to hypercoagulable status.101 Although these viral diseases are not a worldwide threat, patients with stroke are considered to be at risk of these diseases.

**Research Needs and Gaps**

Despite advances in our understanding of nontraditional risk factors for stroke, the clinical utility of these factors remains unclear because of limited published data comparisons with traditional risk factors and a dearth of dedicated clinical trials aimed at assessing the effect of controlling these novel factors of stroke occurrence. The prevalence and predictive value of nontraditional risk factors and event triggers should be examined. Guiraud et al102 systemically reviewed 26 studies of 12 potential triggers and found that the majority of studies were dedicated to alcohol abuse and clinical infection, and other triggers have been far underinvestigated.

Recurrent strokes are often of the same cause as the preceding index stroke. Relative importance of a certain risk factor may differ depending on the underlying stroke mechanism. Previous studies including meta-analysis revealed an important difference in the risk factor profiles depending on the causes of ischemic stroke.103–105 Therefore, continuous efforts are needed to demonstrate the causes of stroke and to control subtype-specific risk factors in patients with ischemic stroke/TIA.

Control of traditional and nontraditional risk factors early in the life may be important. Most published studies have focused on the risk factor in the elderly or middle aged. One recent study showed that the risk of stroke was associated with the proportion of residence in stroke belt in adolescence, suggesting the importance of childhood health circumstances in long-term stroke risk.106 Further studies are needed evaluating risk factors during early in the life. Social efforts are mandatory to control nontraditional risk factors (eg, childhood obesity) and triggering factors (eg, air pollution), whereas control of traditional risk factor could be basically clinic base.

Beyond the Framingham stroke risk score and the aforementioned nontraditional risk factors, prediction of future stroke may improve with genetic risk assessment. Previous candidate gene association studies have identified genes associated with strokes. However, these results were difficult to
replicate, and stroke subtypes were not considered.\textsuperscript{107} Recent genome-wide association study have shown more reliable results, especially when stroke subtypes were considered. Meta-analysis of genome-wide association study on ischemic stroke identified the \textit{ZFHX3} gene on chromosome 16q22 as a locus specifically associated with atrial fibrillation and cardioembolic stroke.\textsuperscript{108,109} Another study identified risk variation associated with cardioembolic stroke on chromosome 4q25 near the \textit{PITX2} gene.\textsuperscript{110} For atherothrombotic stroke, the 9p21 locus\textsuperscript{111} and the \textit{HDAC9} gene on chromosome 7p21.1112 were recently identified. For lacunar stroke, several genetic loci have been identified for spopadic lacunar stroke and single-gene disorders causing cerebral small vessel diseases.\textsuperscript{113,114} With these results, there have been efforts to generate a genetic risk score for ischemic stroke, but further studies are needed because the improvement in clinical risk prediction with genetic models was found to be small.\textsuperscript{115,116}

### Conclusions

Control of traditional risk factors is the cornerstone of stroke prevention. This strategy is clearly working with improvements in lifestyle modification (eg, lower smoking rates) and effective medications (for treating blood pressure and hyperlipidemia) resulting in recent clear reductions in stroke incidence.\textsuperscript{1,2} However, with aging populations in many countries, prevailing obesity epidemics, greater air pollution, and possibly more psychosocial stress,\textsuperscript{2,117,118} to make further gains in stroke prevention, more attention needs to be paid to identifying and controlling nontraditional risk factors. Nontraditional risk factors should be considered for testing and inclusion in stroke risk models. It is conceivable that control or avoidance of at least some of these factors may further reduce the personal and societal burden of stroke.

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### Disclosures

None.

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한국어판

지난 십년 동안 몇 개의 국가에서 뇌졸중의 발병이 감소한 것은 고무적인 일이지만,1-6 비전통적인 위험인자와 관련된 치료는 여전히 관심을 끌고 있는 주제이다.7-9 뇌졸중 발생률은 전 세계적으로 증가하고 있지만,10-14 이는 비전통적인 위험인자와 관련이 있다.15-17

비전통적 위험인자

최근에는 뇌졸중의 발병과 관련된 비전통적 위험인자들이 재평가되고 있다. 이는 뇌졸중의 유병률을 낮추는 데 있어 중요한 역할을 할 수 있다는 것이다.18-20

검색 전략과 선택 기준

이 리뷰에서 우리는 Framingham 연구와 같은 연구에서 이용한 인자들과 고지질혈증을 전통적인 위험인자로 선정하였다. 나머지 위험인자들은 생물학적으로 위험인자와 뇌졸중 발병과의 관계를 그럴듯하게 설명할 수 있는 경우 비전통적 위험인자로 정의하였다. 우리는 stroke, cerebral infarction, cerebrovascular, risk factor, trigger 등의 검색어를 이용해서 PubMed와 ClinicalTrials.gov를 검색하여 2015년 1월까지 영어로 출간된 문헌들을 찾았다. 그 외에도 관련된 논문과 리뷰문에 문헌을 참고하였다. 특수한 상황이 있으면서는 비전통적 위험인자들의 지표가 상당히 일관되지 않았다. 무작위 대조시험에서 고혈압, 당뇨, 고지질혈증, 흡연, 심방세동, 경동맥협착증 등을 치료하면 허혈뇌졸중이나 일차성혈증발작(transient ischemic attack, TIA)의 발병이 감소하며, 역학연구가 이들이 뇌졸중의 발병과 전향적으로 연관되어 있는 것을 보여주었으므로 이들은 뇌졸중의 위험인자로 인정되어야 한다. 이는 뇌졸중의 예방에 의미가 있을 것이다.21-23

비전통적 위험인자

이러한 연구들로, 뇌졸중의 위험요인들은 임상적으로 유의한 수준으로 증가하고 있다. 이를 반영하여, 최근에는 뇌졸중의 위험요인들이 더 많이 주의를 끌고 있는 추세이다. 이러한 분야에서는, 뇌졸중의 위험요인을 더욱 신중하게 고려해야 할 필요가 있다.
팥병(chronic kidney disease, CKD), 영양 또는 식이 등이 있다. 또 심리적 스트레스, 환경요인, 약물 및 음주 등을 포함하는 특정 요인에 대한 폭로가 병태생리학적 과정에 일시적이고 단발적인 강력한 효과를 발휘하여 뇌졸중이나 TIA의 발병을 조장할 수 있다. 그러나 새로운 위험인자와 새로운 유발인자를 구분하는 것은 종종 어려운 일이지만 이런 상황에서 노출되는 양상(예를 들면 급박함)과 뇌졸중 발생의 시간적 간격관계 및 이런 상황의 심각도를 고려하면 이런 구분을 하는데 도움이 될 것이다.

비만과 대사증후군

지난 몇 십 년 동안 비만과 당뇨가 전세계적으로 만연하게 되면서 대사증후군 환자의 수가 급격히 증가하였다. 대부분 연구들은 비만이 뇌졸중의 발병과 관련이 있다는 것을 발견했다. 체질량지수가 1 증가할 때마다 허혈뇌졸중의 발병률이 약 5% 증가하며, 정상 체질량 지수인 20 kg/m^2에서부터 거의 선형적으로 증가한다.

Weight reduction in overweight or obese individuals may reduce stroke risk because of favorable effects on blood pressure, cholesterol, and glycemic control. A recent large pooled analysis showed that about three quarters of the excess risk of stroke with high body mass index is mediated by combination of these traditional risk factors, which can be the target of intervention in addition to maintenance of optimum body weight. However, there is a paucity of high-quality data on effect of weight loss interventions on risk of vascular events.

The Action for Health in Diabetes (Look AHEAD) study is the only randomized trial adequately designed to assess the role of a behavioral intervention for weight loss on vascular event risk. However, the modest weight loss achieved in Look AHEAD (ie, 6% of initial body weight) did not reduce risk for vascular events, and at this time, it can only be assumed that more substantial weight loss may have a significant effect on risk of vascular events. Indeed, results of a large nonrandomized, controlled cohort study of bariatric surgery reported a reduction in the incidence of stroke (adjusted hazard ratio, 0.66; 95% confidence interval, 0.49–0.90).

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The Insulin Resistance Intervention After Stroke (IRIS) trial will determine whether treatment of insulin-sensitizing drugs (eg, pioglitazone) improves cardiovascular outcomes of nondiabetic, insulin-resistant patients with stroke/TIA.

수면장애호흡(Sleep-Disturbing Breathing) 및 폐쇄수면무호흡

Recent studies have suggested that poor quality of sleep and daytime sleepiness may be linked to vascular events. Patients with stroke/TIA have a high prevalence of obstructive sleep apnea (OSA; 50%–70%). OSA may be under-recognized in patients stroke; 1 study showed that most patients did not have typical clinical features of OSA, such as obesity and...
폐쇄수면무호흡(obstructive sleep apnea, OSA; 50%–70%)의 유병률이 높다.28 OSA는 뇌졸중 환자에서 진단이 잘 안되고 있음을 의미한다.29 OSA의 위험도가 높은 급성뇌졸중 환자에게 수면다원검사를 권한다.30 뇌졸중 환자에게 수면다원검사를 한 최근의 연구에서 내피기능장애와 동맥경직은 수면장애 환자에서 관찰되었다.31 수면장애호흡과 연관되어 있었고,31 수면장애호흡은 뇌졸중에 의한 결과일 가능성이 있는 것이 관찰되었다.32,33

만성염증 질환

류마티스관절염 환자에서 볼 수 있는 만성염증은 죽상경화의 발생과 진행에 있어서 중요한 역할을 한다.34 류마티스관절염은 한 장기(예를 들어 손관절)에 국한된 염증이지만, 전염증성 사이토카인은 체순환으로 분비되어 산화스트레스, 인슐린저항성, 내피기능 장애 등을 일으킨다.34 항류마티스제를 이용하여 염증을 억제하면 CVD 발병을 감소시킬 수 있을 것이다.34

기타 질환

심장동맥질환

만성콩팥병

소혈관질환(small vessel disease)이라는 비슷한 해부학적, 기능적 특징을 공유하고 있어서 콩팥과 뇌가 혈관손상에 공히 취약하기 때문에 CKD는 뇌졸중의 발생 가능성을 높이며 대뇌혈관질환 및 인지기능장애와 강한 연관이 있다.33,34 염증체계적소화(estimated glomerular filtration rate)가 60 mL/min per 1.73 m² 미만인 환자들에게는 허혈뇌졸중의 위험도가 높다고 알려져 있다.35,36

식이와 영양

영양부족과 과영양은 모두 뇌졸중을 조장할 수 있다. 비타민(예를 들면 항산화비타민, 비타민D, 엽산), 칼슘, ω-3지방산 등 영양을 보충해 주는 것은 뇌졸중의 예방에도 도움이 된다.46 이런 결과는 음식(예를 들면 생선) 섭취가 뇌졸중 발생에 미치는 영향이 음식 속의 한 가지 성분(예를 들면 긴사슬 ω-3 지방산)에 의해 매개되기보다는 다양한 영양소의 상호작용에 의한 것이라고 생각한다.47 관찰연구(REGARDS 연구), 임상시험 (PREDIMED[PrediMed Prevention With Mediterranean Diet] 연구), 메타분석은 지중해식단(과일, 채소, 견과류, 전곡, 올리브유를 많이 섭취하고 생선을 적당히 섭취하며 붉은 고기는 적게 섭취)이 낮은 허혈뇌졸중의 위험도가 낮음을 보여준다.48–50 전통일식 같은 다른 식단도 허혈뇌졸중의 낮은 발생률과 상관이 있으나 좀 더 연구가 필요하다. 지난반과 동물성 단백질을 적게 섭취하는 것은 아마도 아시아인에게 혼합혈뇌졸중의 낮은 발생율과 상관이 있는 것 같다.51,52 또한 같은 식단 섭취가 뇌졸중의 병태생리에 들면 혈압 강
하)에서 차지하는 역할에 대한 연구들이 속속 나오고 있고, 52, 53 뇌졸중 및 합병증 예방에 대한 무작위시험(식이 섭취 또는 보충)이 필요하다.

정신사회적 스트레스
정신사회적 스트레스는 허혈뇌졸중이나 TIA를 유발하는 것 같고, 인구기반위험(the population-attributable risk)은 4.7%이다. 9 중년 및 노년 성인에 대한 인구기반코호트연구(Multi-Ethnic Study of Atherosclerosis)와 노년 인구에 대한 인구기반코호트연구(Chicago Health and Aging Project)에서 높은 수준의 심리적 스트레스는 뇌졸중 발병과 연관이 있었고 이는 잘 알려진 전통적 위험인자로 설명할 수 없다.54, 55 불안, 공격성, 작업긴장도 등 다양한 정신사회적 스트레스가 뇌졸중 발병 증가에 기여하였다.56, 57 정신사회적 스트레스와 사회적 스트레스는 급성뇌졸중의 쇠도와도 연관되어 있을 수 있다. 동일본대지진(2011년)에 의한 대 피해후 4주 동안 남성 노인에서 뇌경색의 발병이 2배 이상 증가했고 그 이후에는 재난 직전의 수준으로 감소하였다.58

우울증, 피로, A형 행동
우울증은 뇌졸중의 독립적 위험인자라고 알려져 있다. 59 그러나 우울증이 직접적으로 뇌졸중을 일으키기보다는 동반질병이나 과거의 무증상뇌혈변화와 관련이 있을 수 있다는 주장들도 있다. 그림에도 불구하고 최근에 나온 전형적 연구의 대부분에서 메타분석 두 개는 우울증 증상이 추후의 뇌졸중 발병과 관련이 있음을 보여주었다.60 우울증은 심장혈관질환, 심장병, 혈소판응집, 전신염증, 건강에 나쁜 생활방식, 흡연, 알코올, 운동을 일으키는 것으로 알려져 있다. 우울증 또한 뇌졸중 발병과 관련이 있다.61 우울증은 뇌졸중을 일으키는 행동도 있으며 다른 치료와 유사한 비과학적인 치료도 있다.62, 63 치아예방 및 치주건강을 유지하는 것은 뇌졸중 발병을 감소시켰다.64

감염
폐렴클라미디아(Chlamydia pneumoniae), 위염균(Helicobacter pylori), 거대세포바이러스 같은 특정 감염체들은 내피를 침범하여 뇌 및 목의 죽상경화를 일으킨다.92-94 또한 최근의 감염(특히 호흡기감염 및 균혈증)은 죽상경화뇌졸중과 관련이 있는데 이는 감염체가 뇌졸중을 촉발하는 역할을 한다는 것을 보여주었다.95, 96 감염병은 치료가 가능하다면 이 림 발병은 개선의 여지가 있다는 것을 나타낸다. 최근의 연구에서는 치과적 항생제에 대한 무작위대조시험은 효과가 없는 것으로 나왔다.97, 98 이러한 진료법이 세계적인 위험일 가능하지만 이러한 치료법들이 뇌졸중의 발생을 감소시키는 것으로 알려져 있으나 이는 과학적 근거가 없다.99 이러한 발병 방안이 되는 것으로 알려져 있다.

추가 연구 필요성
비전통적 뇌졸중 위험인자에 대한 우리의 지식이 발전하고 있지만 전통적 위험인자와 비교하여 발표한 자료가 부족하고 이런 새로운 위험인자를 조사할 때의 효과를 주목적으로 한 신생영역이 부족하기 때문에 이러한 인자들의 임상적 유용성은 불확실하다. 비전통적 위험인자와 질병 발생요인의 유병율과 예측력에 대하여 연구가 필요하다. Guiraud 등은 12개의 가능성이 있는 축복요인에 대한 26개 연구를 체계적으로 리뷰하여 대부분의 연구가 알코올과 악화적 영향을 가진다고 보고하였다. 이 연구의 논리는 이에 대한 추가 연구가 필요하다.
생긴다. 기저의 뇌졸중 기전에 따라서 특정 위험인자의 상대적인 중요성이 달라질 수 있을 것이다. 메타분석을 포함한 기존 연구들은 혈혈뇌졸중의 원인에 따라서 위험인자 양상에 중요한 차이가 있다는 사실을 발견했다.103-105 따라서 뇌졸중의 원인을 찾고 혈혈뇌졸중 또는 TIA 환자에서 특이적인 위험인자를 조절하려는 지속적인 노력이 필요하다.

전통적 또는 비전통적 위험인자를 점검할 때 조절하는 것은 중요할 것이다. 대부분의 발표된 연구들은 노령이나 중년의 위험인자에 초점을 맞추었다. 최근의 한 연구는 청소년기에 뇌졸중이 얼마나 거주했는지가 뇌졸중의 발병과 관련이 있다는 사실을 보여주어서 장기의 뇌졸중 발생위험에 있어서 소아건강환경이 중요함을 시사하였다.106 젊었을 때 위험인자를 평가하는 추가적인 연구가 필요하다. 비전통적인 위험인자(예를 들면 소아비만)는 축발요인(예를 들면 대기오염)을 조절하려면 사회적인 노력이 필요하고 전통적인 위험인자를 조절하려면 기본적으로 진료소가 중심이 되어야 한다.

Framingham 뇌졸중 위험점수와 앞서 언급한 비전통적 위험인자 외에 유전적 위험평가를 이용해서 미래의 뇌졸중을 예측하는 능력을 향상시킬 가능성이 있다. 과거의 후보유전자관련연구(candidate gene association study)는 뇌졸중과 연관이 있는 유전자를 찾았다. 그러나 이런 연구결과들은 재현이 어려웠고 뇌졸중 아형을 고려하지 않았다.107 최근의 전장유전자관련연구(genome-wide association study)는 특히 뇌졸중아형을 고려할 때 더 신뢰성 있는 연구결과를 내고 있다.

허혈뇌졸중에 대한 전장유전자관련연구의 메타분석은 16q22 염색체에 위치한 ZFHX3 유전자가 심방세동 및 심장성색전뇌졸중과 특이적으로 연관되어 있는 유전자 자리임을 밝혔다.108,109 다른 연구는 PITX2 유전자 인근의 4q25 염색체가 심장성색전뇌졸중과 관련이 있음을 발견하였다.110 최근의 전장유전자관련연구는 단일유전자질환(single-gene disorder)을 발견했다. 이런 연구결과를 이용해서 혈혈뇌졸중에 대한 유전적 위험점수를 만드는 노력이 있지만 유전적모델을 이용한 임상적 위험예측의 개선 정도는 작아서 추가적인 연구가 필요하다.115,116

결론
전통적 위험인자의 조절은 뇌졸중 예방의 초석이다. 이런 전략은 생활방식 개선(예를 들면 흡연을 감소) 및 효과적인 약물(혈압 및 고지질혈증의 치료)에 힘입어 확실히 효과를 내고 있으며 뇌졸중 발생이 극명한 환자에게 확실히 감소하는 결과를 낼 것이다. 그러나 많은 국가에서 노령화하는 인구 구조와 비만의 만연, 대기오염 증가, 정신사회적 스트레스증가에 고려할 때 뇌졸중 예방에 있어서 더 성과를 내려면 비전통적 위험인자를 발견하고 조절하는 것이 더 많은 관심을 쏟아야 할 필요가 있다. 7,117,118 비전통적 위험인자들은 뇌졸중위험모델 안에 포함될 수 있을지 검증하는 것을 고려해야 한다. 이런 인자들의 일부라도 조절하거나 회피한다면 뇌졸중의 개인적, 사회적 부담을 경감할 가능성이 있다.

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Key Words: chronic kidney disease ▪ depression ▪ inflammation ▪ obesity ▪ risk factors ▪ sleep apnea syndrome ▪ stroke