Lifestyle is Not the Only Cause of Stroke—Risk Factors Recently Attracting Attention—

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Abstract: Cerebrovascular disease (stroke) remains the most common disease in Japan and other Asian countries despite the decrease in stroke mortality. It was expected that the incidence of stroke would decrease in line with the mortality rate, but it has not. The major causes of stroke include hypertension, diabetes, and hyperlipidemia, while alcohol, smoking, obesity, hyperuricemia, and polycythemia are other risk factors. All of these factors are closely related to lifestyle. In some cases, however, factors unrelated to lifestyle or generally ignored to date are involved in the etiology of stroke, particularly in young adults. Lipoprotein(a), C-reactive protein, infection with Chlamydia pneumoniae, anti-phospholipid antibodies, and genetic factors are typical risk factors for stroke that are not related to lifestyle. Homocysteine and hyperinsulinemia are also risk factors for stroke, although they are related to lifestyle to some extent. In this article, risk factors for stroke other than the conventional lifestyle-related factors are discussed briefly, mainly based on data obtained from patients whom we have examined. Our findings have emphasized that when risk factors unrelated to lifestyle are combined with lifestyle-related factors, there is a synergetic effect on the development of stroke.

Key words: Risk factors for cerebral infarction; Stroke in young adult; Lifestyle-related disorder; Stroke and genetics

Introduction

Cerebrovascular disease (stroke), along with heart disease, remains the second or the third leading cause of death after malignancy despite the recent remarkable decrease in mortality. Moreover, the proportion of patients treated for stroke, as well as the prevalence of stroke, has remained unchanged or even tended to increase.
In Japan, despite the decrease in mortality, the incidence of stroke has not yet decreased so much, so stroke remains a typical national disease. Indeed, it seems to be a great achievement of preventive medicine that stroke is becoming milder than before. Because there is still no effective therapy for a completed stroke, however, prevention of stroke or control of risk factors is very important.

Do All Strokes Stem from Lifestyle?

Hypertension, diabetes, and hyperlipidemia are the well-known major causes of stroke. There is no doubt that all these conditions, as well as drinking, smoking cigarettes, obesity, hyperuricemia, and polycythemia, are risk factors closely related to lifestyle. An individual’s lifestyle seems to influence even multiple risk factor syndrome (synonymous with syndrome X or the deadly quartet), which is a risk factor for atherosclerosis and a current focus of attention. Overnutrition and stress are thought to play a role in the accumulation of fat in various organs, producing the basis for pathological changes of the atherosclerosis.

However, stroke is not necessarily a lifestyle-related disease in all cases. There is even a possibility that causes unrelated to lifestyle will become more predominant if our lifestyle is modified in the future. Not only do strokes develop in the elderly, but also in relatively younger adults aged 45 or below. In a survey that we performed several years ago, younger adults accounted for about 25% of patients with cerebral infarction. In a survey that we performed several years ago, younger adults accounted for about 25% of patients with cerebral infarction. Stroke in younger adult arose from risk factors closely related to lifestyle in only about one fourth of them, but the causes were unrelated to lifestyle in the remaining three fourths. Even among patients older than 45 years, the primary cause was not one of the well-known risk factors in about one third of them.

Among the risk factors for ischemic cerebrovascular disease, those not directly related to lifestyle will be discussed briefly in this article.

When Should Special Risk Factors Be Considered?

Uncommon risk factors should be considered in stroke patients particularly under the following conditions: 1) relatively young patients (aged 45 or less), 2) the absence of any common risk factors such as hypertension, diabetes, or hyperlipidemia, 3) a family history of frequent recurrent stroke, 4) frequent recurrence of strokes over a short period, and 5) coexisting symptoms of dementia, collagen disease, or severe or frequent headache.

Risk Factors to Be Considered

(1) Lipoprotein (a)

The first risk factor to be discussed is lipoprotein (a), which has attracted attention recently. Lipoprotein (a) (Lp (a)) is an LDL-like lipoprotein that has gained attention as a substance which may link thrombus formation and atherosclerosis. According to a study performed at my department, the plasma Lp (a) level is normally 10–20 mg/dL or less, but the mean level is as high as 28 ± 20 mg/dL in atherothrombotic cerebral infarction, and is particularly high in younger adults with stroke.

Each person has a rather constant level of plasma Lp (a) that remains unchanged throughout life, except during childhood, and this level is defined by autosomal dominant inheritance. Independence of diet and other lifestyle factors characterises Lp (a). Because about half of the individuals with high plasma levels of Lp (a) have no other risk factor for cerebral infarction, it can be considered as a single genetic risk factor for stroke. The plasma level can be measured easily, so Lp (a) is one factor to be assessed in patients with cerebral infarction.

(2) Homocystine

A disease called homocystinuria is known
was significantly increased in individuals who developed myocardial infarction or cerebral infarction during the study period. It has also been reported that the outcome of cerebral infarction is poor if CRP is elevated at the onset. Although the importance of CRP has been underrated in the past, it can be considered as a risk factor or as a predicting factor for stroke that is independent of lifestyle. However, it seems inappropriate to simply regard CRP itself as the only culprit in such patients.

(4) Chlamydia pneumoniae infection

There may be several microbial agents that cause infections related to stroke. Among them, Chlamydia pneumoniae infection has attracted attention recently. Chlamydia pneumoniae is a relatively new species of Chlamydiae that was established in 1989. It is found worldwide as a major causative agent of respiratory tract infections such as pneumonia, bronchitis, and pharyngitis. Antibodies have been reported to be positive in about 40–50% of adults in Europe and the United States. In Japan, the positive rate in the elderly seems to be as high as 70%.

Yamashita has demonstrated immunoreactivity to Chlamydiae in more than half (55%) of the atherosclerotic lesions from patients with severe stenosis of the internal carotid arteries and has confirmed the presence of many Chlamydial elemental bodies in atheromatous plaques by electron microscopy. He also performed multivariate analysis and reported that Chlamydia pneumoniae infection is an independent risk factor for stroke. In Europe and the United States, it has been reported that antimicrobial agents such as azithromycin were effective in preventing the progression of atherosclerosis in patients with ischemic heart disease. More than one large-scale clinical study on this topic is still in progress.

(5) Antiphospholipid antibodies

It is widely known that patients with connective tissue diseases or so-called collagen
diseases are predisposed to cerebral infarction or cerebral venous thrombosis while they are young. In particular, systemic lupus erythematosus (SLE) is not only associated with cardiogenic cerebral infarction, but is also frequently associated with anti-phospholipid-antibody positive cerebral infarction. Furthermore, cerebral infarction with positive anti-phospholipid antibody not infrequently occurs in the absence of SLE. If anti-phospholipid antibodies such as anti-cardiolipin antibodies and lupus anticoagulant are measured particularly in female patients with frequent recurrence of cerebral infarction, it may be possible that their unknown cause of stroke becomes evident.

Data collected by my group showed that anti-phospholipid antibodies were positive in 8.8% out of 273 patients who had cerebral infarction without SLE, and more than one third of them had no other risk factors such as hypertension or diabetes. Based on these results, anti-phospholipid antibodies were also concluded to be an independent risk factor for cerebral infarction. A follow-up study performed for an average of 7 years demonstrated that the recurrence and mortality rates were significantly higher among patients having high anti-phospholipid antibody titers. A normal activation of protein C is thought to be responsible for the development of cerebral infarction in patients with positive anti-phospholipid antibody.

Other coagulation disorders

Not only the protein C abnormality described above, but also disorders of the coagulation and fibrinolysis system such as deficiency of protein S or antithrombin III, and congenital defects of plasminogen, may cause cerebral infarction, particularly in young persons. One of these components of the coagulation and fibrinolysis system was abnormal in as many as 28 out of 77 cerebral infarction in younger adult that we studied. Consequently, these risk factors should be assessed in cerebral infarction of unknown cause in younger adult. The details will be described elsewhere because space is limited. A s coagulation disorders caused by abnormalities such as those described above are only transient in some cases of cerebral infarction in younger adult, however, I would like to emphasize the need to start evaluating for these factors in the acute phase and to repeat the investigations at intervals.

Are Genetic Factors Involved in Stroke?

As the last subject, I would like to discuss the genetic aspects of cerebral infarction briefly, although this is not directly related to lifestyle. The familial occurrence of cerebral aneurysm, which is the major cause of sub-arachnoid haemorrhage, is well known. In addition, Sekiyama in my department has reported the possibility that the A poE 4 gene is involved in the development of atheromatous lesions in the carotid arteries and other major arteries. Moreover, Tachikawa in my department has demonstrated that the mutant α-1-antichymotrypsin 1 gene, which we found several years ago, is strongly involved in ischemic cerebrovascular disease, particularly lacunar infarction. Furthermore, Kario et al. reported that the gene for angiotensin-converting enzyme is involved in ischemic cerebrovascular disease secondary to hypertension. In the near future, as a consequence of progress in genetic studies, the genetic aspects of this disease will be further elucidated.

Conclusion

Even apart from genetic aspect, the evaluation of risk factors not directly related to lifestyle should be also conducted thoroughly, particularly in younger patients with cerebral infarction. Some of the causative disorders are treatable, if they are detected before stroke occurs. Detection of these factors is important
for both physicians and patients from the viewpoint of primary and secondary prevention of stroke.

Finally, I would like to emphasize that lifestyle modification should not be disregarded, because even risk factors unrelated to lifestyle seem likely to potentiate the role of conventional risk factors in the development of stroke. Furthermore, even if conventional risk factors are predominant, the concurrent involvement of other factors should be considered, if necessary.

Because space was so limited, the risk factors for cerebral haemorrhage could not be addressed in this paper and only some of the recently highlighted factors for cerebral infarction were discussed.

REFERENCES


