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Recent Advances in the Development of Therapeutics to Reduce Brain Damage After Stroke

*Chung Y. Hsu, MD, PhD, Professor and Head, Cerebrovascular Disease Section,
Department of Neurology, Washington University School of Medicine, St. Louis, MO*

Abstract

This presentation will first address the impact of stroke on the health of general population in the United States, with special emphasis on Asian Americans, including the Chinese. Risk factors of stroke will then be reviewed. Preventive and therapeutic measures to reduce the probability of developing stroke among people with risk factors will be discussed. Advances in understanding the biochemical mechanism of neuronal death after stroke have been made in the past decade, leading to the development of new drugs that are highly effective in animal models of stroke. It is likely that these therapeutic agents will be available for treating stroke in the near future. Finally, an overview of roles of several neurotrophic factors in restoring brain function after stroke will be given.

Stroke is the third leading cause of death in most industrialized countries. The #1 and #2 killers are heart diseases and cancer, respectively. In the United States, there are approximately half a million new cases of stroke each year. Recent First Families affected by stroke include Franklin Roosevelt, John Kennedy's father, Pat Nixon, Nancy Reagan's father, George Bush's mother, Hillary Clinton's father. Yearly death toll of stroke is approximately 150,000 in the United States. Stroke is the leading cause of disability. Currently there are approximately 2 - 3 million U.S. citizens disabled by stroke. The direct and indirect financial loss from stroke is estimated to exceed \$20 billion a year in the United States. The incidence and prevalence of stroke among Chinese in North America have yet to be studied. It is known that the incidence of stroke among the non-whites is substantially higher than the whites in the United States. Stroke, not heart disease, is the leading cause of cardiovascular diseases in Asian countries. Thus one can expect that Asian Americans including Chinese immigrants, are likely to be more vulnerable to stroke than heart diseases. Risk for developing stroke increases with aging. Retired citizens have a much higher stroke rate than the general population. In addition to age, the following factors have been identified:

1. History of previous stroke;
2. Hypertension;
3. Heart disease or abnormal heart rhythms;
4. Diabetes;
5. High cholesterol levels;
6. Smoking;
7. Birth control pills;
8. Cancer;

9. Family history of stroke;
10. Blood diseases

The annual mortality rate in the United States has declined in the past two decades. The reduction in stroke incidence over the same period was less striking. The lowering of stroke mortality has been largely attributed to the early detection and management of hypertension. Unfortunately no drugs have been proven to be effective in curing stroke or restoring brain function once a person is affected by stroke. The best medical strategy is still prevention. Early identification and treatment of risk factors listed above continue to be the mainstay in stroke prevention.

Several multicenter clinical studies in the past decade have identified a number of interventions that are effective in reducing the probability of developing stroke in selected patient populations. Patients with transient ischemic attacks (TIAs) may benefit from long-term administration of antiplatelet agents such as aspirin or ticlopidine. Among patients with TIAs who have significant stenosis (>70%) of the carotid artery on the appropriate side, carotid endarterectomy may be more effective in the prevention of stroke as compared to the best medical management. Coumarin, an anticoagulant, has also been shown to reduce the probability of developing stroke in patients with non-vascular atrial fibrillation.

In the past decade, advances have been made in the understanding of the biochemical mechanism of brain injury after stroke. Investigators in this country and abroad have identified that excitatory neurotransmitters, particularly glutamate, to be neurotoxins under a variety of pathological conditions including cerebral ischemia. Glutamate is released from neuronal terminals into the extracellular space after cerebral ischemia. Excessive amount of glutamate opens several channels or gates at the surface of the neurons allowing massive influx of sodium and calcium. These ions, particularly calcium, activate a number of biochemical cascades leading to neuronal dysfunction and death. The pivotal role of glutamate in causing brain damage after stroke has been well established. A few glutamate antagonists are effective in preventing or reducing neuronal injury in animal models of stroke. Novel compounds that are effective in blocking the toxic effects of glutamate are being developed for stroke therapy. It is likely that effective new drugs will be available to reduce brain damage or disability after stroke in the near future.

Cerebral ischemia - reperfusion is frequently accompanied by the generation of toxic single oxygen species, so called free radicals. Free radicals are toxic to organs including the brain. Drugs that are capable of neutralizing the toxic effects of free radicals are also being developed for the management of stroke.

For those who have already been disabled by stroke, recent understanding of the roles of neurotrophic factors in maintaining viability and promoting regeneration also offer hope that restoration of function after stroke will become a reality in the future.

Stroke prevention - Oriental style

Pathological studies of the cerebral vasculature indicate that atherosclerosis along the vessels including those supplying the brain advances gradually with age. Studies of

cerebrovascular pathology have shown a racial difference in the distribution of atherosclerotic lesions. In the Caucasian population, the pathology is likely to be in a proximal location such as the bifurcation of the carotid arteries in the neck. This type of lesion is accessible to surgical correction. Among the Orientals the vascular degeneration is more likely to occur within the brain. These lesions are usually not amenable to surgical intervention. The Orientals are also more likely to develop small vessel diseases that may cause different types of stroke including the hemorrhagic one.

Among the important observations of the East-West discordance in stroke, none is more significant than the finding that Orientals are known to have greater incidence of hemorrhagic stroke. Hemorrhagic strokes carry a substantially higher mortality rate than the non-hemorrhagic ones. The cause of this racial difference is not known, but cholesterol level may be an important marker in this respect. In Japan, most patients with hemorrhagic strokes were noted to have lower cholesterol levels, in the 145-155 mg/dL range. In the Western population, low cholesterol is rare but is also associated with a higher risk of hemorrhagic stroke. Thus, the increased incidence of hemorrhagic stroke among Asians may be related to the notion that cholesterol level is generally lower in this population. This speculation appears to be supported by epidemiological studies of Eskimos who consume more fish and are associated with lower cholesterol levels, lower incidence of coronary heart disease, but higher incidence of stroke presumably hemorrhagic in nature.

For stroke prevention, Orientals may need to take a different approach than that advocated for Caucasians. In the West, the prevention of cardiovascular disease is primarily targeted at atherosclerosis that affects coronary arteries, carotid arteries, and other major arteries. For the Orientals, the risk may be more in the smaller vessels that are likely to be associated with hemorrhagic stroke. Lowering cholesterol below certain levels (below 160 mg/dL, as has been seen in a substantial percentage of Asians) may not be a right strategy as far as stroke prevention is concerned. It appears that with industrialization and accompanying changes in dietary habit toward Western style, the East-West discordance may gradually disappear. Knowing the possible causes of the racial difference in the prevention of cardiovascular diseases, however may still help in the development of better preventive measures, especially for the Orientals.

When I can look Life in the eyes, Grown calm and very coldly wise, Life will have given me the Truth, And taken in exchange - my youth. -- Sara Teasdale, "Wisdom"