Cystatin C, Associated With Hemorrhagic and Ischemic Stroke, Is a Strong Predictor of the Risk of Cardiovascular Events and Death in Chinese

Li Ni, MD; Jiagao Lü, MD; Ling Bo Hou, MD; Jiang Tao Yan, MD; Qiao Fan, BSMT; Rutai Hui, MD, PhD; Katherine Cianflone, PhD; Wei Wang, MD, PhD; Dao Wen Wang, MD, PhD

Background and Purpose—Cystatin C, a serum measure of renal function, has been reported as a strong predictor of risk of death and cardiovascular events in elderly people. We investigated the association between cystatin C and first-ever stroke and evaluated the predictive value of cystatin C in cardiovascular events and death from all causes based on the outcomes of a 5-year follow-up.

Methods—We recruited 293 stroke patients (199 cases of cerebral infarction, 94 cases of cerebral hemorrhage) and 894 controls. For each measure, the study population was divided into quintiles.

Results—Total plasma cystatin C levels were significantly higher in patients than controls. Higher cystatin C levels were directly associated with a higher risk of stroke. As compared with the first (lowest) quintile, the hazard ratios (and 95% CIs) for stroke were as follows: second quintile, 1.97 (1.07 to 3.64); third quintile, 2.71 (1.50 to 4.90); fourth quintile, 3.79 (2.12 to 6.75); fifth quintile, 6.38 (3.60 to 11.32). Follow-up of the patients and controls also showed that high cystatin C levels were associated with high prevalence of cardiovascular events or death from all causes.

Conclusions—Elevated cystatin C levels were independently associated with both ischemic and hemorrhagic stroke, and cystatin C was a strong predictor for the risk of cardiovascular events and death. (Stroke. 2007;38:3287-3288.)

Key Words: cerebral hemodynamics ■ cerebral infarct ■ cerebrovascular disease ■ clinical neurology ■ cystatin C ■ prognosis ■ risk factors ■ stroke

Cystatin C, an alternative measure of renal function, is now accepted as a strong predictor of cardiovascular events and death in most ethnic groups.1 But its role in different subtypes of stroke has not been fully demonstrated yet. In this study, we investigated the relationship between cystatin C and both ischemic and hemorrhagic stroke, and assessed the potential of cystatin C as a marker to predict cardiovascular events and death from all causes in persons with or without stroke via a 5-year follow up.

Materials and Methods

Subjects

This is a multicenter study for assessment of risk factors for stroke sponsored by the Ministry of Science and Technology of China. Patients and controls were recruited from November 2000 through June 2002 from 5 hospitals in Wuhan, China. Cerebral infarction and hemorrhage were included. Other types of stroke as well as severe systemic diseases such as collagenosis, endocrine and metabolic diseases (except diabetes mellitus [DM]), tumors, and serious chronic diseases were excluded. Controls were selected from inpatients with minor illnesses from other departments and local community-based residents free of neurological diseases following the same exclusion criteria.

Follow-up visits of patients and controls were performed by telephone or by household contact every 2 years. Cardiovascular events included myocardial infarction, stroke and transient ischemic attack (TIA).

Biochemical Variables and Cystatin C Assay

Plasma samples were obtained from participants after a fast and stored at $-80^\circ$C. Plasma biochemical parameters were assayed using an automatic analyzer (7060, Hitachi). Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).

Statistical Analyses

Differences in categorical variable distribution between groups were assessed by $\chi^2$ test. Differences for continuous variables among the study groups were assessed by ANOVA test. The association of either plasma cystatin C or creatinine with stroke and its subtypes, as well as the predictive value of cystatin C on outcomes in patients and controls during a 5-year follow-up period, was analyzed by binary logistic regression.

Results

Characteristics of Patients and Controls

As expected, stroke patients had a higher prevalence history of hypertension and diabetes, coronary heart disease, ciga-
rette smoking, alcohol intake, higher blood pressure and waist-to-hip ratio, higher levels of plasma homocysteine and lower levels of HDL cholesterol. Compared with controls, the mean plasma cystatin C level was significantly higher in stroke patients (1.22 ± 0.51 versus 0.98 ± 0.39 mg/L, P < 0.001). Cystatin C levels of cerebral infarction and hemorrhage were 1.27 ± 0.29 and 1.07 ± 0.35 mg/L, respectively (supplemental Table I, available online at http://stroke.ahajournals.org).

Association Between Cystatin C and Different Subtypes of First-Ever Stroke

Patients and controls were pooled to represent an integrated population study, and for each measure the total population was divided into quintiles. After adjustment for age, sex, body mass index, presence or absence of hypertension, presence or absence of a history of myocardial infarction, as compared with the first (lowest) quintile, the hazard ratios (and 95% CIs) for stroke were as follows: second quintile, 1.97 (1.07 to 3.64); third quintile, 2.71 (1.50 to 4.90); fourth quintile, 3.79 (2.12 to 6.75); fifth quintile, 6.38 (3.60 to 11.32). Elevated cystatin C levels were strongly associated with stroke and its subtypes of cerebral infarction and hemorrhage. However, when plasma creatinine was evaluated, only the highest creatinine subgroup had a significantly increased risk of cerebral infarction (supplemental Table II, available online at http://stroke.ahajournals.org).

Risk of Cardiovascular Events or Death From All Causes

The incidence of second cardiovascular events or death from all causes in the patients during the follow-up period was determined for each of the 5 categories of cystatin C. Stroke patients within the lowest cystatin C quintile had the lowest incidence of cardiovascular events (11.5%) and death from all causes (9.6%), whereas patients with cystatin C levels in the other 4 quintiles had a higher incidence of cardiovascular events (23.1% to 26.9%) or death from all causes (19.2% to 36.5%). Controls quintiles were pooled as follows: quintile 1 and 2 were defined as the low-risk category, quintile 3 and 4 were defined as an intermediate-risk category, and quintile 5 was defined as a high-risk category. The incidence of cardiovascular events or death from all causes was 4%, 5.6% and 13.6%, respectively (supplemental Table III, available online at http://stroke.ahajournals.org).

Discussion

It is believed that impaired renal function is an important risk for clinical stroke. Cystatin C, which is constitutively expressed and secreted constantly by all nucleated cells, is a better estimate of renal function, particularly within the “normal” range of kidney function. In this study, even a slight increase in plasma cystatin C level was associated with an increased risk for clinical stroke, other cardiovascular events and death from all causes.

Several reasons may explain why cystatin C levels may be an important risk factor for stroke and other cardiovascular events. First, high cystatin C levels may reflect the duration and severity of other established risk factors. For instance, people with a long history of uncontrolled hypertension may have poorer renal function, and such people have a tendency for cardiovascular events. Second, reduced kidney function itself may be a risk factor for cardiovascular events. Third, cystatin C, as an inhibitor of cysteine proteases, plays an important role in the pathogenesis of atherosclerosis. High levels of cystatin C may directly affect the process of vascular wall remodeling by regulating the balance of proteolytic and antiproteolytic activities. Finally, cystatin C may have direct toxic effects that contribute to its association with risk of stroke and other cardiovascular events.

Although there was no overall significant difference between hemorrhagic patients and controls, following analysis based on the level of cystatin C, the highest level of cystatin C was nonetheless associated with an increased prevalence of hemorrhage. We hypothesize that, after hemorrhage, there may ensue a physiological response that enhances the catabolism of cystatin C, to protect against proteases, such as cysteine protease, which could degrade vascular substances. This may also explain why, compared with quintile 1 of cystatin C, the adjusted odds ratios of quintile 5 were 8.74 for cerebral infarction but only 2.37 for cerebral hemorrhage (supplemental Table II).

In summary, our findings indicated that elevated cystatin C levels were independently associated with both ischemic and hemorrhagic stroke in Chinese subjects. Furthermore, the plasma cystatin C level may represent a strong predictor for the risk of cardiovascular events and death in persons with or without stroke.

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Disclosures

None.

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