

Editorial Comment

Family History of Stroke: An Old and Still Unproven Risk Factor

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Many studies have examined whether a family history of hypertension and/or stroke increases an individual's risk of a stroke (1–6), but the results have been inconsistent. The significance of family history in predicting the occurrence of strokes is still controversial. Nevertheless, mass screening programs worldwide include questions about an individual's family history of diseases. On the other hand, a mass screening guideline for metabolic syndrome released by the Japanese Ministry of Health, Labour and Welfare in 2008 does not recommend using a family history questionnaire.

Stroke has a multifactorial etiology, where hypertension is a major attributable risk for stroke. The genetic heritability of risk factors, family sharing of cultural/environmental and lifestyle factors, and the interaction between genetic factors and environmental factors could play significant roles in the development of hypertension and the onset of a stroke (7). The fraction of the variance of an individual's blood pressure level that can be explained by inheritance has been estimated to be approximately 40%, even for twins (8). The source of the residual fraction has scarcely been explored.

Does a parental history of stroke increase an individual's risk of stroke? Are responses to family history questionnaires used in clinical settings or large-scale epidemiological surveys reliable? The unreliability of an offspring's memory may bias a family history that was obtained as a response to a questionnaire. Before computed tomography was widely available in clinical settings in the early 1980s, misclassification of stroke diagnosis was a source of bias. A large fraction of strokes that occur at an early stage can be attributed to familial factors (9). Some countries, including Japan, have experienced a dramatic change of lifestyles since the 1950s.

Compared to old people, younger individuals are likely to share a larger proportion of lifestyle and environmental factors with their parents. Therefore, the predictability of family history would be more significant among younger subjects.

Evidence from the Framingham Study of parents and offspring could give some answers to the above questions. The subjects' parents' cardiovascular events were validated objectively in a cohort study (not self-reported by offspring). The presence of parental cardiovascular disease (CVD) increased the CVD risk for middle-aged offspring. The risk was more prominent among offspring with premature parental CVD (5).

The evidence obtained from the Framingham Study seems to be conclusive. However, there is a gap between the information about family history in the Framingham Study and the evidence in other large-scale epidemiological studies and actual clinical settings. Many factors that contribute to the occurrence of strokes (including family history) have shown various degrees of association in different populations. Genes in the Japanese population have changed little in the last 100 years. On the other hand, life expectancy, the major causes of death, and lifestyle-habits (including food intake and physical activity) have changed dramatically. A shorter life expectancy in the parent's generation could have reduced the risk of suffering from CVD in old age.

Is a family history significantly associated with the occurrence of stroke in Japan? A Japanese study in the early 1970s showed that a family history of stroke was significantly related to cerebral hemorrhage (1). Questionnaires and interviews concerning family history have been recommended for use in many mass screening programs (10). Subsequently, however, few studies have reported an association between

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family history and stroke.

Kadota *et al.* in this issue of *Hypertension Research* examined the relationship between stroke mortality and family history of hypertension and stroke using a nationwide public health center study in Japan (11). For all strokes, a family history of hypertension significantly increased the risk among men aged ≥ 60 years and women aged < 60 years after adjustment for blood pressure. Men with parents diagnosed with hypertension showed a higher risk of cerebral infarction, whereas a family history of stroke showed a borderline significant protective effect against cerebral infarction. An individual's response to the question about their parents' hypertension could partially contribute to identifying high-risk groups for stroke. In contrast, a history of stroke in an individual's parents did not accurately predict the occurrence of strokes in their offspring. A dramatic decrease in the cause-specific mortality of strokes during the past century may have had some effect on the results. As the authors have discussed, some people who did not get infectious diseases and, thus, lived longer were therefore at risk of suffering a stroke.

Kadota *et al.* provide some answers to the question about family history and have contributed to stroke prevention in Japan. However, some questions remain unanswered, and other issues have arisen. In the Kadota's study, premature stroke death of parents was not examined, and mortality was used as an endpoint (rather than incidence). Considering the low mortality rate in Japan after the first stroke (12), the ability of family history to indicate the likelihood of stroke in the Japanese population might be underestimated. We need further studies to determine the actual significance of family history in stroke prevention.

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