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Secular trends in the incidence, risk factors, and prognosis of transient ischemic attack in Japan: The Hisayama Study

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ABSTRACT

Background and aims: We aimed to investigate secular trends in the incidence, risk factors, and prognosis of transient ischemic attack (TIA) in a general Japanese population.
Methods: Two cohorts consisting of stroke-free Japanese individuals aged ≥40 years in 1961 (n = 1621) and 1988 (n = 2646) were followed up for 24 years. The associations of potential risk factors with the development of TIA were estimated by a Cox proportional hazards model. The influence of TIA on the risk of total stroke over the subsequent 10 years was compared between the sub-cohorts of subjects with TIA and age- and sex-matched control subjects from each cohort.
Results: During follow-up, 28 subjects in the 1961 cohort and 34 in the 1988 cohort experienced TIA. The age-standardized incidence of TIA was significantly lower in the 1988 cohort than the 1961 cohort (0.66 *vs.* 1.01 per 1000 person-years, p = 0.02). While elevated systolic blood pressure was significantly associated with the risk of TIA in both cohorts, glucose intolerance and higher serum cholesterol levels were associated with TIA risk only in the 1988 cohort. The subjects experiencing TIA had approximately 7–8-fold higher risks for the 10-year incidence of total and ischemic strokes compared with the corresponding control subjects without TIA both in the 1961 and 1988 sub-cohorts, and the relative risks were not significantly different between sub-cohorts.
Conclusions: Our results suggest that the incidence of TIA decreased during the past half century, probably due to the spread of antihypertensive treatments in the general Japanese population.

1. Introduction

Transient ischemic attack (TIA) is a clinically important symptom as an early warning sign of imminent stroke. Several population-based observational studies [1–14] have estimated the incidence of TIA, but most of them [2–9,11–14] were performed in Western countries. In Asia, there has only been our previous report in conjunction with the Hisayama Study [15], in which we examined the incidence of TIA in the period from 1961 to 1981 in a general Japanese population. Over the last half century, the prevalence and severity of cardiovascular risk factors in Japan, such as hypertension, diabetes, dyslipidemia, and smoking, have dramatically changed [16], and the management of these risk factors has been improved. Consequently, the incidence rate of stroke has been decreased in Japan [16]. Therefore, it can be assumed that the incidence of TIA in the Japanese population has also changed with time. However, this issue has not been adequately addressed in Western countries [1–3], and has been almost completely ignored in Japan. Moreover, no studies have examined the secular trends in the association between risk factors and the development of TIA and in the risk of subsequent stroke after TIA. The aim of the present study was to estimate the secular trends in the incidence, risk factors, and prognosis of TIA in a Japanese community, Hisayama,

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using two cohorts separated by an interval of 27 years.

2. Materials and methods

2.1. Study population

The Hisayama Study is a population-based cohort study of cardiovascular diseases (CVD) established in 1961. The town of Hisayama, where the epidemiological study has been ongoing, is located in a suburb of the Fukuoka metropolitan area in Kyushu Island, Japan. According to the national census, the population of the town was approximately 6500 in 1960 and 8400 in 2010. The age and occupational distributions and nutrient intake levels in the residents of Hisayama have been similar to those of Japan as a whole during the past half century [16]. A detailed description of this study was published previously [15–18]. A total of 1658 residents of Hisayama aged ≥40 years participated in the health examination in 1961 (participation rate in this age group: 90.1%) [16,17]. We excluded 4 participants who died and 8 who moved away from the town before the start of follow-up, and 25 who had a history of stroke, and selected the remaining 1621 participants as the 1961 cohort. Similarly, a total of 2742 Hisayama residents aged ≥40 years underwent the health examination in 1988 (participation rate: 80.9%) [18]. After excluding 6 participants who died before the start of follow-up and 90 who had a history of stroke, the remaining 2646 participants were included in the 1988 cohort. This study was approved by the Kyushu University Institutional Review Board for Clinical Research, and written or oral informed consent was obtained from all the participants.

2.2. Risk factors

Blood pressure was measured three times in a supine position in 1961 and in a sitting position in 1988 using a mercury sphygmomanometer after an at least 5-min rest. Korotkoff phase 5 was taken as the diastolic blood pressure unless the sounds persisted at zero, in which case Korotkoff phase 4 was recorded. The mean of the three measurements was used in the present study. Hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive agents. In 1961, glucose intolerance was defined by a full stomach test or 100-g oral glucose tolerance test (OGTT) in participants with glycosuria as described previously [16]. In 1988, we performed 75-g OGTT for almost all participants aged 40–79 years, or a fasting or postprandial glucose measurement for others [18]. In this cohort, glucose intolerance, which included both diabetes and prediabetes, was defined as fasting plasma glucose concentration ≥6.1 mmol/L, 2-h postload plasma glucose concentration ≥7.8 mmol/L, postprandial plasma glucose concentration ≥11.1 mmol/L, or use of antidiabetic agents. Serum total cholesterol levels were measured by the modified Zak-Henly method in 1961 and by the enzymatic method in 1988 [16]. Hypercholesterolemia was defined as serum total cholesterol ≥5.7 mmol/L. Overweight was defined as body mass index ≥25 kg/m^2. Atrial fibrillation was diagnosed by electrocardiogram (Minnesota code: 8–3). Smoking habits and alcohol intake were categorized as either current use or not. Current drinking was also categorized as light (1–33 g/day) or excessive (≥34 g/day) drinking according to daily ethanol intake.

2.3. Follow-up survey

The participants of each cohort were followed up prospectively for 24 years, from November 1961 to October 1985 for the 1961 cohort, and from December 1988 to November 2012 for the 1988 cohort, by the same method. In the annual follow-up examinations, physicians and research nurses asked each participant whether he/she had experienced clinical symptoms of CVD events (TIA, stroke, and coronary heart disease). For participants who did not undergo a regular examination or who moved from the town, vital status and clinical information of CVD were collected by mail or telephone interviews. In addition, in order to collect the information of potential CVD events more exhaustively, we established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. When a participant died, autopsy examination was performed at Kyushu University if consent for autopsy was obtained. All of the available information about potential CVD events or deaths among the study participants were collected and reviewed by physician members of the Hisayama Study, including stroke neurologists and cardiologists, to determine the occurrence of CVD under the standardized diagnostic criteria. All CVD events were adjudicated by means of a panel discussion among member physicians. Except for the deceased cases, only two participants in the 1961 cohort and no participants in the 1988 cohort were lost to follow-up during the follow-up periods.

2.4. Definition of TIA

TIA was defined as a sudden onset of nonconvulsive focal neurological deficit, such as hemiparesis, aphasia, amaurosis fugax, and so on, due to brain ischemia which resolved within 24 h, regardless of the presence or absence of corresponding ischemic stroke lesions on brain imaging or autopsy, according to the Classification of Cerebrovascular Disease III (CVD-III) criteria by the National Institute of Neurological Disorders and Stroke published in 1990 [19]. During the follow-up periods, 28 participants in the 1961 cohort and 34 in the 1988 cohort experienced a TIA event.

2.5. Cumulative risk of stroke after TIA

In order to compare cumulative risks of total stroke and ischemic stroke after the onset of TIA between the two cohorts, we established a sub-cohort consisting of subjects who developed TIA during the 24-year follow-up and control subjects who were randomly selected from the participants without TIA events and matched by baseline age and sex in each cohort (case:control = 1:3). The 1961 sub-cohort included 28 subjects with TIA and 84 control subjects, and the 1988 sub-cohort had 28 TIA subjects (excluding 6 subjects who developed TIA after a stroke event during the follow-up) and 84 controls. Each sub-cohort was followed up for 10 years from the date of TIA onset for each subject with TIA (or the corresponding date for matched control subjects) or until October 1985 or November 2012. Stroke was defined as a sudden onset of focal neurological deficit persisting for >24 years and classified as ischemic stroke and hemorrhagic stroke (intracerebral and subarachnoid hemorrhage) according to the CVD-III criteria [19]. Ischemic stroke events were further divided into lacunar infarction, atherothrombotic infarction, cardioembolic infarction, and other ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment criteria [20], as described previously [21].

2.6. Statistical analysis

The prevalence of risk factors was adjusted for age and sex by the direct method using the distribution in the 1961 cohort as a reference population, and compared between the two cohorts by logistic regression analysis. The mean values of risk factors were adjusted for age and sex and compared between the cohorts by the analysis of covariance. The incidence of TIA was calculated by the person-years method, and the standardization for age was made by