Pathologic Study of Intracranial Large Artery Atherosclerosis in 7260 Autopsy Cases

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Background: Atherosclerotic changes in the cerebral arteries may differ with era of birth. Herein, we analyzed the chronological changes of intracranial atherosclerosis in consecutive autopsy cases. *Methods:* A total of 7260 autopsy cases from 1972 to 2014 were analyzed. Severity of atherosclerosis was classified using a semiquantitative scale of pathologic observation of each artery after formalin fixation: 0 = no stenosis; .5 = fatty streaks but no stenosis; 1 = <50% stenosis; 2 = 50%-90% stenosis; 3 = ≥90% stenosis. The bilateral vertebral, anterior, middle, and posterior cerebral arteries and the basilar artery were scored. The sum of each individual was defined and compared by age at death, sex, and era of birth. *Results:* The atherosclerosis score increased with age at death, as follows: age in the 50s, 0 [0-2]; 60s, 3 [.5-7]; 70s, 5 [2-9.5]; 80s, 6.5 [3.5-11.5]; 90s, 7.75 [4-12]; and 100s, 8 [5.5-13.5] (median value [interquartile range], $P < .0001$). The percentage of cases with a score of 2 or 3 in each artery also increased with age ($P < .0001$). Atherosclerosis score was higher in men than women in their 60s at death, and was higher in women than men in their 80s and 90s at death. In each age at death group (from 60s to 100s), the score declined with later year of birth ($P < .05$). *Conclusions:* Intracranial atherosclerosis advances with age and is more severe in subjects born earlier. **Key Words:** Intracranial atherosclerosis—age—sex—pathology—risk factors—era.

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Introduction

Atherosclerosis of the intracranial large arteries, such as the internal carotid artery, anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), vertebral artery (VA), and basilar artery (BA), is one of the main causes of ischemic stroke.[1] Intracranial large artery atherosclerosis (ICLAA) occurs more frequently in Asian, Hispanic, and African populations compared with the Caucasian ethnic group.[2-4] Therefore, ICLAA may be an important pathologic condition in clinical settings in Japan. Several large autopsy series also found that ICLAA was associated with age, sex, hypertension, and diabetes mellitus.[3,5-8]

Recent studies have used noninvasive imaging modalities such as magnetic resonance angiography, computed tomographic angiography, and transcranial Doppler ultrasonography, rather than catheter angiography, for evaluating ICLAA in institution- or community-based

healthy cohorts or ischemic stroke cases.[9-17] However, there are some discrepancies between findings obtained by noninvasive imaging modalities and pathologic observations.[18] Therefore, further studies examining the pathology of ICLAA at autopsy are required.

The risk factors for ICLAA include age,[5-7,11,12,17] race,[2,3] hypertension,[3,5,6,12,17] diabetes mellitus,[3,10-12,18,19] and metabolic syndrome.[19,20] Of these, modifiable risk factors such as hypertension, diabetes mellitus, and metabolic syndrome can be well controlled by changes in lifestyle and medication. In the present study, we hypothesized that the ICLAA pathology of an individual is affected by the era of birth. Indeed, treatment of vascular risk factors, food trends, and living environment have changed over the last 50 years. Further, according to the Honolulu Heart Program,[5] the incidence of ICLAA declined from 1965 to 1983. However, these data were obtained from only 198 cases, with a short observation period over 30 years. In our brain bank (Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology [TMGHIG], the Brain Bank for Aging Research, Tokyo, Japan), ICLAA has been regularly observed by neuropathologists in autopsy cases from 1972 to present.[21] Thus, the aim of the present study was to determine the chronological changes in ICLAA in consecutive autopsy cases in Japanese subjects.

Methods

Case Selection

We analyzed 7260 autopsy cases from subjects ≥50 years old at the time of death from a total of 7307 consecutive Japanese autopsy cases at our Brain Bank for Aging Research. Autopsies were performed in our institute from May 1972 to March 2014. Our brain bank is an official division of the TMGHIG, a general hospital in the northern part of Tokyo that provides advanced medical services for aging individuals.

Severity of ICLAA

From 1972, we assessed ICLAA using autopsy materials after formalin fixation of the brain. Severity of atherosclerosis was evaluated using a semi-quantitative scale based on macroscopic cross-sectional observation. We examined the proximal portion of the ACA, MCA, and PCA, the intracranial VA bilaterally, and the BA. The most severe site of each artery was evaluated and classified as follows: 0 = no stenosis; .5 = fatty streaks but no stenosis; 1 = <50% stenosis; 2 = 50%-90% stenosis; 3 = ≥90% stenosis on the axial section of vessels. The fatty streak was identified at the time of brain dissection by neuropathologists. The score of each vessel was defined as the "severity score" (SS). The sum of the SS in each artery for each case was defined as the "atherosclerosis score" (AS). Thus, the AS ranged from 0 to 27 in all cases. The findings were reviewed by at least 2 neuropathologists at the time of brain dissection. All data were stored in the brain bank database by neuropathologists.

Data Analysis

Clinical data on age at death, birth date, sex, and cause of death were obtained from medical charts, summaries, or databases. We grouped the age at death into 10-year blocks (50s, 60s, 70s, 80s, 90s, and 100s), and compared the AS data between the age groups, including the effect of sex. We also grouped the birth year into decades (1870s, 1880s, 1890s, . . . 1960s) and compared AS data between these groups. If a case had an SS of 2 or 3 in at least one artery, the case was considered as having severe atherosclerosis of the intracranial large artery (SA-ICLA). The percentage of individuals with SA-ICLA was also calculated for the age at death groups and year of birth groups. We conducted a substudy based on whether the cause of death was stroke or not.

Statistical Analysis

As SS and AS are ordinal scale data without a normal distribution, data were presented as median values and interquartile range or frequencies (%). A difference by age at death and era of birth was analyzed by the Kruskal–Wallis test. A difference by sex was determined by the Mann–Whitney U test. A difference of the rate of cases with SA-ICLA was determined by the chi-square test. A P value less than .05 was considered statistically significant. All statistical analyses were performed using JMP 11 (SAS Institute, Cary, NC).

Consent and Institutional Review Board

The brain samples used in this study were registered to the Brain Bank for Aging Research, and the relatives of the deceased provided informed consent to perform these studies. The Brain Bank for Aging Research was approved by the ethics committee of the TMGHIG.

Results

Case Selection

From 1972 to 2014, we analyzed 7307 consecutive autopsy cases in our brain bank. As our brain bank is focused on aging individuals, the number of cases <50 years old at death was small. Thus, we only analyzed cases with an age ≥50 years at death in this study (total of 7260 cases; 3723 men, 3537 women; 51.3% men). A summary of cases is shown in Table 1. The mean age of all cases was 79.5 ± 8.7 years. The majority of cases were in their 70s and 80s at death, whereas a low number of individuals were born in the 1870s, 1950s, and 1960s. The rates of major causes of death were stroke in 9.8% of patients, cardiovascular disease in 8.5%, and malignant neoplasm in 31.7%.