

# 学位論文の要旨

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学位論文名 A Prospective Study of Asymptomatic Intracranial Atherosclerotic Stenosis in Neurologically Normal Volunteers in a Japanese Cohort

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## 論文内容の要旨

### INTRODUCTION

Atherosclerotic stenosis of major intracranial arteries is one of leading causes for ischemic stroke in Asia. However, the long-term prognosis of asymptomatic intracranial atherosclerotic stenosis (ICAS) in healthy volunteers has not been fully examined. Furthermore, there has been no longitudinal study investigating the long-term prognosis of ICAS in combination with the role of asymptomatic brain lesions. We performed a prospective study to examine whether ICAS is associated with subsequent stroke onset independent of other risk factors, including asymptomatic brain lesions, in addition to general vascular risk factors in a large number of healthy, elderly Japanese volunteers.

### MATERIALS AND METHODS

We originally enrolled a total of 3,161 consecutive Japanese volunteers who voluntarily underwent a medical examination of the brain at the Health Science Center in Shimane between December 2000 and December 2010. The inclusion criteria for this prospective study were as

follows: no history of neurological or psychiatric disorders, including stroke, no abnormalities on neurological examination, and the provision of informed consent to participate in this study. Magnetic resonance imaging (MRI) was performed with a 1.5-T scanner (Symphony Ultra Gradient, Siemens). Vascular stenosis of the main intravascular arteries was assessed: <25% reduction of an arterial diameter was graded as normal; 25 – 49% reduction as mild stenosis; 50 – 74% reduction as moderate stenosis; 75 – 99% reduction as severe stenosis; and no opening as occlusion. Because the volunteers with severe stenosis or occlusion were subjects to medical interventions, we included only subjects with mild or moderate ICAS. The middle cerebral artery (MCA), the intracranial portion of the ICA, the anterior cerebral artery (ACA), the posterior cerebral artery (PCA), and the basilar artery (BA) were evaluated. Silent brain infarction, periventricular hyperintensity (PVH), and the presence of deep and subcortical white matter lesions (DSWMLs) were also assessed. SBI was defined as a focally hyperintense lesion >3 mm in diameter on T2WI, corresponding to a hypointense lesion on T1WI. DSWML and PVH were evaluated separately, because PVH is found adjacent to the ventricles, whereas DSWML is found away from them. PVH was graded using the Fazekas' grading scale.

We excluded volunteers from the analysis who developed intracerebral hemorrhage or subarachnoid hemorrhage during the follow-up period ( $n = 10$ ). We could not make any contact with 344 volunteers during the follow-up period. As a result, we analyzed data from a total of 2,807 volunteers (1,497 men and 1,310 women; mean age,  $62.0 \pm 8.5$  years), resulting in an 88.8% follow-up rate. Clinical information obtained included age, sex, history of hypertension (defined by the use of an antihypertensive agent, systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg), diabetes mellitus (defined as a fasting blood glucose level  $\geq 126$  mg/dL, HbA1c  $\geq 6.5\%$ , or a history of treatment for diabetes mellitus), and dyslipidemia (defined as a low-density lipoprotein cholesterol level  $\geq 140$  mg/dL, triglyceride level  $\geq 150$  mg/dL, high-density lipoprotein cholesterol level  $< 40$  mg/dL, or a history of treatment with lipid-lowering medication). A smoker was defined as any subject whose smoking index exceeded 200. Regular alcohol consumption was defined as more than 58 mL of alcohol consumed per day. Group differences were analyzed using the Student's *t*-test or the chi-squared test. Comparisons of cumulative event-free rates for volunteers with or without ICAS were done using Kaplan–Meier curves with the log-rank test. Cox proportional hazards ratios (HRs) were fitted to ICAS data after adjusting for age and other potentially confounding factors. Statistical analysis was performed with the SPSS software package (version 22, IBM Corp., Armonk, NY, USA).

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

## RESULTS AND DISCUSSION

Asymptomatic ICAS was observed in 166 volunteers (5.9%), of whom 42 had moderate and 124 had mild ICAS. Moderate and mild stenoses were observed in 1.5 and 4.4% of volunteers, respectively. Significant risk factors for ICAS were older age and a history of hypertension and/or dyslipidemia. During a mean follow-up period of 64.5 months, 32 (1.1%) volunteers had a cerebrovascular event: ischemic stroke in 26 (0.89%) volunteers and TIA in 6 (0.21%) volunteers. Seven strokes occurred in the ICAS group, whose stroke incidence rate was higher than that in the non-ICAS group (0.78 vs. 0.18% per year). We performed a Kaplan–Meier analysis with the log-rank test for volunteers with or without ICAS. There was a significantly higher incidence of ischemic stroke events in volunteers with mild or moderate ICAS compared to that in those without ICAS ( $P < 0.001$ ). In the Cox regression analysis, volunteers with mild or moderate ICAS had significantly higher incidences of ischemic stroke events than those without ICAS after adjusting for age.

Results from the current longitudinal cohort study demonstrated that even mild to moderate asymptomatic ICAS was an independent risk factor for future ischemic stroke in a healthy population. Many studies have confirmed that there is a high risk of vascular events in patients with symptomatic ICAS who had already experienced stroke. Thus, incidental identification of asymptomatic ICAS in healthy volunteers should not be ignored, even when the stenosis is mild.

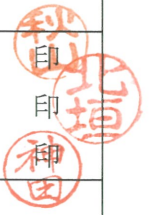
Elderly people with SBI and DSWMML have been reported to be at a highly increased risk of stroke, which could not be explained by other major stroke risk factors. We conducted a logistic regression analysis that incorporated asymptomatic brain lesions into the regression models, and the results showed that asymptomatic ICAS was still a significant predictor for ischemic stroke events. The current study demonstrated that asymptomatic ICAS and DSWMML independently contributed to future stroke occurrence. To the best of our knowledge, this is the first study to demonstrate asymptomatic ICAS as an independent risk factor for future stroke, even in healthy volunteers, after adjusting for asymptomatic brain lesions, which are strong risk factors for ischemic stroke. The control of risk factors for ICAS is important for preventing stroke associated with ICAS lesions, because most risk factors are treatable. The current study demonstrated that age, hypertension, and dyslipidemia were independent risk factors for asymptomatic ICAS.

## CONCLUSION

Mild to moderate asymptomatic ICAS was a significant risk factor for future stroke, independent of asymptomatic brain lesions, in a healthy Japanese population. Mild to moderate ICAS might be a therapeutic target for stroke prevention.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

脳卒中患者における頭蓋内動脈硬化性狭窄病変（ICAS）の臨床的意義はこれまで多くの検討がなされてきたが、健常人における無症候性ICASの意義に関しては検討が殆どなされていない。今回、一般的な血管リスク因子に加えてICASおよび無症候性脳病変が、その後の脳卒中発症に関連しているかどうかを検討するために前向き研究を行った。対象は、脳卒中を含む神経学的異常所見がなく、本研究に参加するインフォームドコンセントが得られた2,807人（男性1,497人、女性1,310人、平均年齢62.0歳）である。関連因子として年齢、性別、喫煙歴、飲酒歴、高血圧症、糖尿病、脂質異常症を検討した。血管狭窄はMR Angiographyで評価し、動脈直径の狭窄率によって、25%以下を正常、25～49%を軽度狭窄、50%～74%を中等度狭窄、75～99%を重度狭窄とした。さらに無症候性脳梗塞病変（SBI）、脳室周囲高強度（PVH）、深部皮質下白質病変（DSWML）についても評価を行った。エンドポイントは、脳梗塞および一過性脳虚血発作を含む脳血管イベントの発生と定義した。本研究では、無症候性ICASは166人（5.9%）で観察され、そのうち中等度ICASは42人、軽度ICASは124人に認められた。ICASの有意な危険因子は年齢、高血圧、脂質異常症であった。経過中（平均観察期間64.5か月）32人に脳血管イベントが見られ、非ICAS群に比しICAS群は有意にイベントが多かった（ $P < 0.001$ ）。その年間発症率は非ICAS群で0.18%に対し、ICAS群では0.78%であった。Cox回帰分析では、イベント出現に対するハザード比は軽度ICAS群で3.04、中等度ICAS群で6.10であった。さらにICASはSBIおよびDSWMLの有無を調整した後においても、虚血性脳卒中イベントの独立した危険因子であった。本研究は、軽度から中等度のICASは、無症候であっても脳卒中の重要な危険因子の一つであることを明らかにした臨床的に重要な研究であり、学位授与に値する。

最終試験又は学力の確認の結果の要旨

申請者は無症候性頭蓋内血管狭窄病変の脳梗塞発症のリスクについて、2,807人の健常人を対象に前向き研究をおこなった。無症候性狭窄病変の脳卒中リスクのエビデンスは少なく、本研究は大変貴重である。関連領域における知識も豊富であり学位授与に値すると判断した。（主査：秋山恭彦）

申請者は2807例の極めて多数例による前向き研究で無症候性の頭蓋内動脈狭窄が有意な脳梗塞発症リスクであることを初めて明らかにした。臨床的に有意義な知見であり、周辺知識も豊富であることから学位授与に値すると判断した。（副査：北垣 一）

申請者は、島根県内の2807人の脳ドック健診受診者から得たデータをもとに疫学的検討を行い、脳血管疾患の発症に無症候性ICASの関連を追跡調査によって明らかにした。研究方法や結果の解釈、また関連領域の知識等についての質問に対し、適切な回答が得られた。博士（医学）の学位授与に値すると判断した。（副査：神田秀幸）