(– 14.8%, n = 528) one year later, and similar variation was seen during the study period. Group C showed no change of ApoB, being 112.1 mg/dl (n = 523) at the start and 112.2 mg/dl (+ 0.1%, n = 274) one year later, and similar variation was seen during the study period. No significant difference was found between the two groups.

Treatment effects on evaluation items

CHD events occurred in 9.2/1,000 patient-years for men and 2.4/1,000 patient-years for women without a history of CHD. CHD events occurred in 55.3/1,000 patient-years for men and 23.6/1,000 patient-years for women with a history of CHD, which was six times higher in men and 10 times higher in women than for those without a history of CHD, respectively. Myocardial infarction occurred in 4.5/1,000 patient-years for men and 0.2/1,000 patient-years for women without a history of CHD, and 8.4/1,000 patient-years for men and 5.7/1,000 patient-years for women with a history of CHD. Table 2 shows the relative risk for the primary and secondary endpoints and the 95% confidence interval (95%CI). Patient numbers for onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, and death of CHD including heart failure and sudden death were 31, 13, 13, and 1 in group P and 16, 16, 3, and 2 in group C, respectively. The adjusted relative risk in group P for CHD events was calculated to be 0.74 (95%CI: 0.47-1.19).

CVD events occurred in 2.4/1,000 patient-years for men and 2.2/1,000 patient-years for women without a history of CHD, and 9.4/1,000 patient-years for men and 3.5/1,000 patient-years for women with a history of CHD. Patient numbers for onset or recurrence of cerebral infarction, onset of cerebral hemorrhage, and death (cerebral infarction or hemorrhage) were 11, 2, 3, and 1 in group P, and 6, 2, 3, and 0 in group C, respectively. The adjusted relative risk in group P for CVD events was calculated to be 0.71 (95%CI: 0.31-1.63). In the cases with a history of CHD, the adjusted risk of group P for CVD events relative to group C was 0.59 (95%CI: 0.35-1.64).

The ratio of CHD events to causes of all deaths was 8%, while cancers accounted for 45% of all deaths. There was myocardial infarction (0.16%), heart failure (0.16%), cerebral hemorrhage (0.16%), cancer (1.01%), trauma or suicide (0.16%), and other diseases (0.39%) in group P. There was myocardial infarction (0.13%), sudden death (0.13%), cerebral infarction (0.13%), cancer (0.53%), trauma or suicide (0.27%), and other diseases (0.40%) in group C. After adjustments, the relative risk in group P for total mortality was calculated to be 0.76 (95%CI: 0.35-1.64).

One man without a history of CHD and 2 men with a history of CHD developed both CHD and CVD. A man and a woman without a history of CHD and 4 men and 2 women with a history of CHD developed CHD and died. Four women without a history of CHD and one man with a history of CHD developed CVD and died.

Compared with the cases without a history of CHD, the cases with it showed an apparent treatment effect of pravastatin on CHD events, CVD events and total mortality.

Study according to the achieved LDL-C levels

As a secondary analysis, the achieved LDL-C level and occurrence of CHD events were investigated. Among 2,039 cases as subjects for analyses, 17 cases without measured LDL-C levels at registration and during the course or in which the LDL-C level could not be calculated due to TG > 400 mg/dl were excluded. To confirm the treatment effect, 26 cases in which CHD events occurred within 180 days after initiation of the study were also excluded. Consequently, 1,996 cases were used for analyses. When only measured LDL-C levels during follow-up were lacking, the baseline levels were adopted. To test significance, the Cox proportional hazard model was used. Adjustment factors included gender, age, family history of CHD, anginal pain, smoking, diabetes, HDL-C level, TG level, and LDL-C level. Table 3 shows the results of a comparison in which the occurrence of CHD events was compared between the group in which the mean LDL-C level during the follow-up period reached the treatment goal and the group in which it did not. The LDL-C treatment goal of 140 mg/dl in the guideline of hypercholesterolemic treatment was made a cut-off as a reference.

In all cases of group P and group C, the adjusted relative risk in the group achieving the goal was 0.63 (95%CI: 0.39-1.02). The occurrence of CHD events

Table 2. Numbers of Events and Age-adjusted Rate for the pravastatin group versus the diet therapy group

Event	Pravastatin (n = 1,290)		Only diet therapy (n = 749)		Adjusted RR (95% CI)‡
	Number of events	Age-adjusted rate†	Number of events	Age-adjusted rate†	
CHD events§	58	9.5	37	12.3	0.74 (0.47-1.19)
CVD events§	17	2.7	11	3.6	0.71 (0.31-1.63)
Total mortality§	26	4.1	12	4.1	0.76 (0.35-1.64)

† Rate per 1,000 patient-years. Calculated by the direct method using the patient-years by 10-year age class in the whole subjects standard. ‡ Based on Cox hazards model controlling for gender, age, serum total cholesterol, serum HDL cholesterol, serum triglyceride, history of CHD, diabetes mellitus and smoking. § The earlier event was counted in the case of concurrent occurrences.

Table 3. Numbers of events and adjusted relative risks for the average LDL-C levels during the follow-up over 140 mg/dl versus those less than 140 mg/dl.

Group	LDL-C (mg/dl)	Number of events	Age-adjusted rate†	Adjusted RR (95% CI)‡
ALL (n = 1996)	< 140	32	6.7	0.63 (0.39-1.02)
	≥ 140	36	8.4	
No history of CHD (n = 1647)	< 140	14	3.7	0.77 (0.37-1.60)
	≥ 140	17	4.3	
History of CHD (n = 349)	< 140	18	18.5	0.53 (0.28-1.01)
	≥ 140	19	35.0	

† Rate per 1,000 patient-years. Calculated by the direct method using the patient-years by 10-year age class in the whole subjects standard. ‡ Based on Cox hazards model controlling for gender, age, serum LDL cholesterol, serum HDL cholesterol, serum triglyceride, family history of CHD, anginal pain, diabetes mellitus and smoking.

tended to decrease. In cases having a history of CHD, the adjusted relative risk in the group achieving the goal was 0.53 (95%CI: 0.28-1.01) and a similar tendency was seen.

Safety

Cancer-related mortality was 2.0/1,000 patient-years in group P and 1.4/1,000 patient-years in group C. Adverse events reported by physicians included increased CPK in the musculoskeletal system, and hepatic dysfunction and increased GOT and GPT in the hepatobiliary system. No serious adverse events were observed in association with long-term treatment with pravastatin.

Discussion

The present study can be characterized as (1) a follow-up study in hypercholesterolemic patients with a low incidence of CHD, including women; (2) using low doses of pravastatin, compared with those in studies in Western countries; and (3) the presence of a control group, despite non-randomization.

The incidence of myocardial infarction was compared between the Holicos-PAT and AFCAPS/TexCAPS. In the AFCAPS/TexCAPS conducted in the USA, which showed the lowest incidence of events among previous major trials, the incidence of myocardial infarction was reported to be 5.6/1,000 patient-years in the placebo group (6). After adjustment for gender on primary prevention, the incidence of events in the present study was about 1/3 that of the above study. The incidence of CHD events in other domestic studies was so low that the annual incidence of myocardial infarction with a serum cholesterol level of 218 mg/dl or higher in Okinawa was 4.6/1,000 person-years for men and 2.2/1,000 person-years for women (18). In the KLIS, in which only male patients were used as subjects, CHD events, including myocardial infarction, coronary angioplasty and bypass operation, heart death, and sudden death, occurred at 5.95/1,000 patient-years in the conventional drug therapy group (13). In the Holicos-PAT, the incidence of CHD events in group C was 5.63/1,000 patient-years. In the J-LIT (19) performed in Japan on patients treated with simvastatin, the incidence of myocardial infarction on primary prevention was 0.86/1,000 patient-years (percentage of men: 32.2%). In the Holicos-PAT, the incidence of myocardial infarction in group P was 1.58/1,000 patient-years (percentage of men: 33.4%). In the Holicos-PAT, the incidence of CHD events was 3.8 times higher in men than in women without a history of CHD and 2.3 times higher than in women with a history of CHD. The incidence of CHD events for those without a history of CHD was 3.8 times higher in men and 1.1 times higher in women. In Japan, the ratio of heart failure to all causes of death is generally comparable to that of CVD-related deaths, and hypercholesterolemic patients are thought to be prone to develop CHD, compared with CVD.

Pravastatin has been used in Japan at a dose of 10 mg/day, up to 20 mg/day. The worldwide dose is double this, and the results of large-scale clinical trials in Western countries have been obtained with doses exceeding those applicable in Japan. The reduction of LDL-C from the pretreatment level was 24% in the present study, demonstrating a reduction of the same degree as that observed in the WOSCOPS and CARE.

This study was not a randomized-controlled trial. The analyses in the non-randomized clinical trial were limited to interpret the results. The effectiveness of the treatment with pravastatin was statistically analyzed by dividing the patients into those treated with pravastatin and those only on diet therapy. TC and LDL-C levels were significantly lower in group P than in group C, and differences in TC and LDL-C levels between the 2 groups were 12.8 and 15.1 mg/dl five years later, respectively. Thus, no significant difference was found in comparisons of adjusted relative risk in events of CHD or CVD, and total mortality. However, when the high risk group with a LDL-C level of almost 180 mg/dl was treated with pravastatin, the LDL-C level could be reduced to that in patients whose level was controlled to less than 150 mg/dl by diet therapy

in terms of events of CHD or CVD and total mortality. Compared with group C, the risk reduction in group P was 26% for CHD events, 29% for CVD events, and 24% for total mortality. The risk reduction rates were similar to those in Europe and the U.S.A. The tendency was most notable in cases having a history of CHD, where the risk of CHD events decreased by 45%. It is unclear why the risk reduction rates for events were comparatively large despite a small difference in LDL-C levels between the 2 groups in the present study. This finding may indicate that there are direct effects of pravastatin, such as a tendency for thrombosis to decrease (20), correcting the oxidation resistance of lipoproteins (21), etc., other than effects related to cholesterol lowering. In cases in which mean LDL-C levels achieved the treatment goal in the secondary analysis, the risk of CHD events decreased. The treatment effect was particularly notable in cases with a history of CHD.

This result supported the results reported in Japan and Western countries. (5, 8, 9)

In this study, no critical events due to administration of pravastatin for a long period were found. Cancer-related mortality was 2.0/1,000 patient-years in group P and 1.4/1,000 patient-years in group C. As for death due to cancer, when the expected number of the cancer deaths in the Japanese based on age (22) was applied to the cases in this study, the incidence was estimated at 2.9/1,000 patient-years in group P and 2.5/1,000 patient-years in group C. The incidence in both groups did not exceed these values.

Conclusion

The present study demonstrates the outcomes of CHD and CVD in hypercholesterolemic patients, including women, revealing a lower incidence of CHD in Japan, compared with Western countries. Pravastatin could be safely used, and it was suggested that the cholesterol-lowering therapy with pravastatin has inhibitory effects on CHD, CVD, and total mortality. The effect was notable in cases with a history of CHD. In a lower risk group such as the Japanese, just how high risk patients showed be identified and treated remains to be studied.

Appendix 1

The following investigators participated in the Holicos-PAT.

Ishikawa prefecture: Akimichi Asano, Yorito Emoto, Noboru Fujino, Shigeo Hamada, Tetsuji Hashiba, Seiji Hayashi, Toshinori Higashikata, Miki Hiramaru, Yuhki Horita, Takayuki Hoshiba, Takahiko Igawa, Masatoshi Ikeda, Akihiro Inazu, Hidekazu Ino, Hideaki Ito, Norio Iwaki, Shigeru Jinkawa, Bunji Kaku, Nobuo Kamon, Akira Kaneto, Ken-ichi Katsuki, Suguru Kawasaki, Yoshihito Kita, Masaru Kitamura, Ichiro Koizumi, Kunio Kondo, Kensyo Konishi, Akira Matsui, Masami Matsumura, Masahiro Minamoto, Yasushi Miyake, Masaji Miyamoto, Kiyoo Mori, Toshinari Mura, Takuro Muramoto, Yuko Murase, Takeshi Nakao, Atsushi Nohara, Hisanori Oiwake, Eizo Okino, Shinsuke Shibayama, Yasushi Shiire, Toshimi Shimada, Tokei Shin, Ryuichiro Soma, Norihiko Sugihara, Takashi Takahashi, Yoshihiro Takayama, Hiroaki Takimoto, Nariaki Terashima, Yoshiki Tokuhisa, Taketsugu Tsuchiya, Ryosei Ueda, Yoshihisa Uetani, Kunimasa Yagi, Shinji Yagi, Jundo Yamaguchi, Masato Yamaguchi, Tsukasa Yamazaki, Haruya Yanase, Kikuo Yasuda, Toshihiko Yasuda, Yoshiaki Yasuda, Masahiro Yonejima, Kohei Yoshimitsu, Akira Yoshimura, Kimiaki Yoshino, Hiroyuki Yoshio

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Event Evaluation Committee: Hiroshi Mabuchi, Junji Koizumi, Masami Shimizu, School of Medicine,Kanazawa University; Susumu Miyamoto, Himi City Hospital; Kouji kajinami, Kanazawa Medical University

Statistician: Hideki Origasa, Toyama Medical and Pharmaceutical University

Appendix 2

Endpoints

1. Angina pectoris – chest pain or discomfort with all of the following characteristics:
   (1) Site must include the sternum (any level)
   (2) Must occur during a time of exertion or

stress and must usually last at least 30 sec
(3) Must on most occasions disappear within 10 min of rest or a decreases in the intensity of exertion
(4) Must usually be relieved in 2-5 min by nitroglycerine

The Reappearance or exacerbation of chest pain or discomfort with characteristics fulfilled by (1–4) was considered as a worsening of angina pectoris, when the event was accompanied with a change of therapy.

II. Event of coronary artery bypass surgery or angioplasty

III. Non-fatal myocardial infarction – any one or more of the following categories using the stated definitions:
(1) Diagnostic ECG at the time of the event
(2) Ischemic cardiac pain and diagnostic enzymes
(3) Ischemic cardiac pain and equivocal enzymes and equivocal ECG
(4) A routine ECG is a diagnostic for myocardial infarction while the previous one was not

IV. Death from CHD including heart failure and sudden death – either or both of the following categories:
(1) Heart death – one or both of the following categories:
(i) Deaths occurring subsequently to definite or suspected myocardial infarction
(ii) Deaths occurring in those with known CHD when no cause other than CHD could be ascribed as the cause of death
(2) Sudden and unexpected death (requires all three characteristics)
(i) Deaths occurring within 1hr after the onset of severe symptoms or having last been seen without them
(ii) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal
(iii) An "unexpected death" occurs only in a person who is not confined to their home, hospital, or other institution because of illness within 24hr of the death

V. Cerebrovascular disease – a diagnosis requires all of the following:
(1) History of recent onset of unequivocal and objective findings of a localizing neurologic deficit documented by a physician
(2) Findings persist longer than 24 hr
(3) The neurologic findings are not referable to an extracranial lesion
(4) Findings of a computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy record to classify the cerebrovascular disease into cerebral hemorrhage or cerebral infarction. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area on the basis of the clinical findings or a stroke for which there was evidence of cerebral infarction at autopsy. Cerebral hemorrhage was classified on the basis of evidence obtained on CT or MRI scan or at autopsy, excluding hemorrhagic conversion of infarction.

VI. All cause mortality

Glossary

I. Ischemic cardiac pain – severe substernal pain having a deep or visceral quality and lasting for 30 min or more

II. ECG (classified by Minnesota Code)
(1) Diagnostic – either of the following must be present:
(i) Unequivocal Q or QS pattern (Code 1-1)
(ii) Q or QS pattern (Codes 1-2-1 to 1-2-7), plus any T-wave item (Codes 5-1 to 5-3)
Only the first criterion applies in the presence of ventricular conduction defects
(2) Equivocal – any of the following must be present:
(i) Q or QS pattern (Codes 1-2-1 to 1-2-7)
(ii) ST junction and segment depression (Codes 4-1 to 4-3)
(iii) T-wave items (Codes 5-1 to 5-2)
(iv) Left bundle-branch block (Code 7-1)

III. Enzymes
(1) Diagnostic enzymes – all of the following conditions:
(i) Creatine kinase, GOT, or lactic dehydrogenase values determined coexistent with the event
(ii) The upper limit of normal for the local laboratory is recorded
(iii) The determined value for one or more enzymes is at least twice the upper limit of the local laboratory
(2) Equivocal enzymes – all of the following

conditions:
(i) Creatine kinase, GOT, or lactic dehydrogenase values determined coexistent with the event
(ii) The upper limit of normal for the local laboratory is recorded
(iii) The determined value for one or more enzymes is elevated but does not fulfill criteria for diagnostic enzymes

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脳卒中後遺症患者のQOL質問票の妥当性について

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背景

QOL(生活の質)というのは、患者本位の医療において重要な位置をしめる。わが国では脳卒中患者が極めて多いが、その後遺症を持った高齢者のQOLを測るツールは今まであまりなかった。米国で開発されたSS-QOL[1](脳卒中患者用QOL調査票)を日本語へ翻訳し、再現性調査により信頼性についてはすでに報告した[2]。

目的

原典SS-QOLの妥当性は米国では検討済みであるが、本研究では日本語版SS-QOLの妥当性を検討することを目的とした。

方法

120名の脳卒中外来患者を対象として、SS-QOLのValidationスタディを平成12年8月に実施した。調査方法は面接者つきの自己記入方式を採用した。付き添い人介助での記入(10%)も可能とした。観察データとしては、日本語版SS-QOL、SF-36 日本語第2版、家族構成・趣味嗜好・地域関与・生きがいなどの情報、外的基準として「脳卒中になる前と現在との比較」データも収集した。なお、すべての患者から文書で同意を得た。検討した妥当性としては、尺度妥当性、構成妥当性、収束・弁別妥当性、領域内一貫性、層別解析等による妥当性である。

SS-QOLは全部で12領域から成り、Self care (SC), Vision (V), Language (L), Mobility (M), Work/Productivity (W), Upper extremity (UE), Thinking (T), Personality (P), Mood (MD), Family roles (FR), Social roles (SR), Energy (E)を含む。各質問は5段階になっている。すなわち、1(ワースト)～5(ベスト)に分布していて、総合点は12領域得点の平均として定義される。

結果

調査対象である120名の平均年齢は70歳で、男性が74%を占めていた。

尺度妥当性の検討から、主としてADLといった身体面のQOLでベストの5点であった患者が25～60%もおり、少し対象が軽症だと高いほうに振れてしまうことが伺われた。一方、精神・社会面のQOLでは10～30%程度で普通であった。

構成妥当性は因子分析で検討したが、全部で8因子(固有値1以上の基準)しか抽出されなかった。また、Self careとVision、MobilityとWork/productivity、EnergyとSocial rolesなどが同一因子に分類された。

身体面の収束・弁別妥当性はMTMM法により十分だと確認できたが、VitalityとEmotionについては特に弁別妥当性が低かった。

領域内一貫性はすべての領域で満足する値を示していた。

感受性あるいは予測妥当性をみるために、脳卒中になる前からの印象度を外的基準として層

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別解析したのが Fig 1 である。「以前より悪化」したと感じる患者は、「不変」と感じる患者よりもすべての領域で QOL が有意に低い結果であった。Tab 1 でさらに患者背景により層別解析を行ったところ、男性や不規則生活の患者で QOL が低く、大家族で QOL が高いことが見られた。また、社会活動によく参加したり、生きがいを強く感じている老人ではより高い QOL を認めた。これらのことから十分な感受性を有すると思われた。

結　論

脳卒中 QOL の日本語版を開発し、その妥当性を断面調査で検討したところ、一部問題点も明らかになったが全体としては十分な結果が得られた。今後一部改良の後、公開へ向けて進めていきたい。

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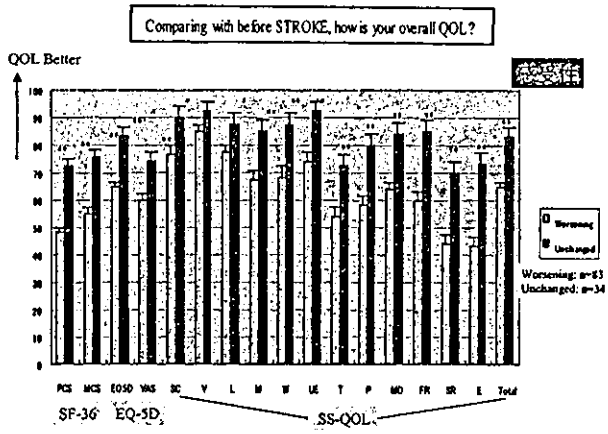

Fig 1　Predictive validity of the Japanese SS-QOL
注：SS-QOL は100点換算した。

Tab 1　Sensitivity by a set of subgroup analyses

項目	カテゴリー	N	PCS	MCS	SS-QOL#	
性別	男性	89	54.7	61.0	67.8	悪化
	女性	32	57.5	62.4	76.0	
年齢	≧７０歳	66	58.6	55.0	70.0	
	＞７０歳	55	58.3	60.0	70.0	
生活	規則的	63	58.5	55.0	71.3	
	中間	44	60.3	56.6	71.3	
	不規則	12	49.5	51.8	61.3	悪化
世帯数	１世帯	71	59.0	56.5	70.5	
	２世帯	35	53.2	48.8	69.5	
	３世帯	10	69.2	66.8	75.5	良好
社会活動	よく参加する	11	75.9	72.8	84.8	
	たまに参加する	27	63.6	61.5	75.8	
	あまり参加しない	34	57.3	52.8	70.8	
	全く参加しない	45	53.4	51.3	63.5	
生きがい	すごく感じている	38	65.6	63.1	78.0	
	少しは感じている	40	54.3	51.3	68.8	
	どちらともいえない	14	61.7	57.9	64.3	
	あまり感じていない	14	52.2	47.1	61.0	
	全然感じていない	5	49.4	50.4	63.0	

#１００点に換算、PCS: SF-36 身体面、MCS: SF-36 精神面

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Transient global amnesia: increased signal intensity in the right hippocampus on diffusion-weighted magnetic resonance imaging

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Abstract We report on a patient with pure transient global amnesia (TGA) whose magnetic resonance imaging (MRI) demonstrated a small region of increased signal intensity in the right hippocampus on diffusion-weighted imaging (DWI). DWI was sensitive and useful for evaluating the early stage of TGA and might help to explain the pathophysiology of TGA.

Keywords Transient global amnesia · Magnetic resonance imaging · Diffusion-weighted imaging

Introduction

Transient global amnesia (TGA) is a syndrome which is characterized by a sudden-onset and transient memory disturbance with preserved alertness, attention and personal identity [1, 2, 3]. Although the pathogenesis and etiology of TGA still remain uncertain, three recent MRI studies [4, 5, 6] reported that diffusion-weighted imaging (DWI) might detect early parenchymal tissue changes, especially in the medial temporal regions. In this paper we present a patient with a transient amnestic attack which fulfilled the established diagnostic criteria of TGA [1, 2, 3], in whom DWI showed a small region of increased signal intensity in the right hippocampus 44 h after the onset. Our current findings and a review of previous reports suggest that DWI might help us to understand the pathogenesis of TGA and might be useful for clinical diagnosis and management.

Case report

A 63-year-old, right-handed retired office worker without a history of migraine, epilepsy or head injury was referred to us with an episode of amnesia. His wife found him well 1 h before the onset, and then he suddenly began to ask repetitive questions about subjects that he should have known about. For example, on seeing a package containing a computer printer that he had ordered 2 days before, he repeatedly asked his wife, "What is in this package?" and "Who ordered this?" He found a current volume of his favorite magazine that he had bought 1 week before and repeatedly asked, "Why is this here?" He understood his wife's explanations but immediately forgot them. He could identify himself and his family members, but he could not remember that he had gone to church earlier in the day. The patient continued to ask repetitive questions of a general physician at the presentation 4 h after the onset. The physician described him as alert, with preserved identity, but amnestic. A brain CT was normal. His amnesia and repetitive questioning gradually resolved. After he had stayed overnight at the hospital, his symptoms subsided except for the loss of the memory during the attack. At the initial presentation to us, 42 h after the onset, he was alert and well oriented. General physical and

neurological examinations were normal. He scored 30/30 on the Mini Mental State Examination (MMSE). The scores on the Wechsler Memory Scale Revised (WMS-R) were as follows: verbal memory index, 110; visual memory index, 106; general memory index, 108; attention index, 90; and delayed recall index, 104. A neuropsychological interview showed that his amnestic gap was from 1 h before to 5 h after the onset of the attack. An electroencephalogram (EEG) was normal. He underwent an MRI examination 44 h after the onset. Images were obtained on a 1.5-T unit capable of echo-planar imaging (GE Signa Advantage version 5). DWI revealed a small region of increased signal intensity in the right hippocampus (Fig. 1D). There was also a corresponding region of high signal intensity on the conventional T2-weighted image (T2WI) (Fig. 1C). He showed no recurrence of amnestic attack. There were no signal abnormalities in any of the sequences of the follow-up MRI examinations 2 weeks and 3 months after the onset (Fig. 2).

Discussion

Though this patient did not undergo a detailed neuropsychological assessment during the attack, the diagnosis was definite TGA based on the clinical diagnostic criteria [1, 2, 3], which consisted of the presence of a witness and absence of the following: clouded consciousness, loss of personal identity, cognitive impairment other than amnesia, and focal neurological symptoms or history of head injury or epilepsy. An important differential diagnosis is epilepsy, but in most patients with epilepsy that resembles TGA, the amnesia lasts less than 1 h [3].

Several neuroradiological studies of TGA patients have been conducted, and recently, the usefulness of DWI in MRI has been discussed. Strupp et al. [4], using DWI, found high signal intensity in the left or bilateral medial temporal regions in patients during or immediately after a TGA attack. The authors found these observations to be consistent with the symptoms of TGA because medial temporal lesions may cause disturbances of episodic memory. They also noted the absence of signal abnormalities in follow-up MRI using T2WI and DWI, and reported that the pathogenesis of TGA is not of an ischemic nature. They attributed the high signal intensity to extracellular edema and interstitial narrowing between the cells caused by physiological neural dysfunction due to spreading depression [7].

On the other hand, Woolfenden et al. [5] described a patient who suddenly developed TGA-like amnesia after cerebral angiography. In the MRI of this patient, DWI and T2WI showed high signal intensities in several areas including the right hippocampus and bilateral occipital lobes. The signal abnormality completely disappeared 2 weeks after the attack. The authors reported that the alteration in the signal intensity was transient because

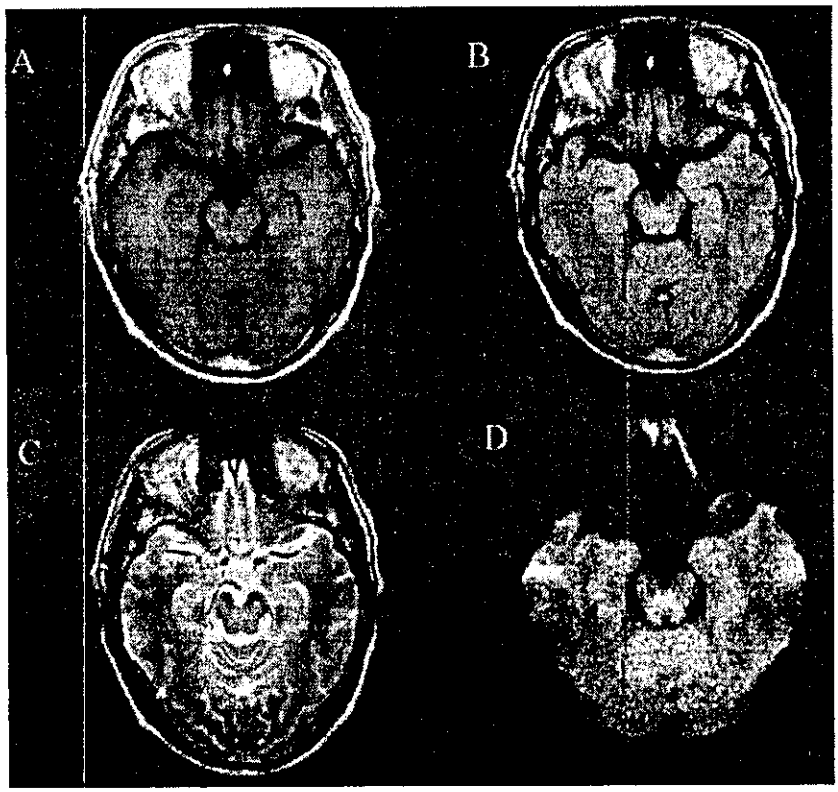

Fig. 1A–D. Initial MRIs acquired 44 h after the onset, showing the same level at a 5-mm slice thickness with 2.5-mm gap covering medial temporal lobe structures. **A** Conventional T1-weighted image (T1WI) (TR/TE/NEX = 500/13/2, FOV: 20×20 cm, matrix: 256×256). **B** FLAIR image (TR/TE/NEX = 9,000/147/1, FOV: 20×20 cm, matrix: 256×256). **C** Conventional T2WI (TR/TE/NEX = 3,000/105/2, FOV: 20×20 cm, matrix: 256×256). **D** DWI (TR/TE/NEX = 2,000/118/1, FOV: 24×24 cm, matrix: 256×256, b-value: 1, 000 s/mm^2). The conventional T1WI (**A**) and FLAIR image (**B**) are almost normal, but the conventional T2WI (**C**) and DWI (**D**) demonstrate the same small regions of increased signal intensity in the right hippocampus

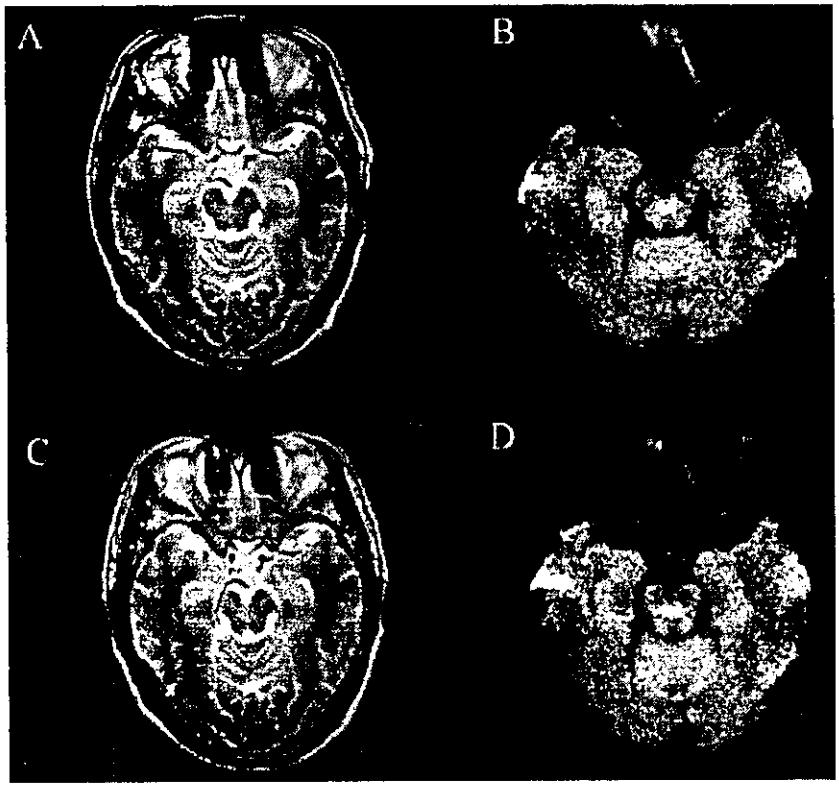

Fig. 2A–D. Follow-up MRIs. The top row (**A, B**) and the bottom row (**C, D**) show the images acquired 2 weeks, and 3 months, after the onset, respectively. None of the sequences shows any signal abnormalities

the infarct area caused by the ischemia was too small to be detected by follow-up MRI. The MRI findings in the current patient were similar to those of Woolfenden et al. [5] in that he had a very small and localized lesion that was observed as a high signal intensity on T2WI.

However, other studies failed to detect signal alterations in magnetic resonance DWI in TGA patients. Ay et al. [6] reported a TGA patient with normal DWI who had vascular risk factors, and Budson et al. [8], using both DWI and perfusion-weighted MRI, also reported a TGA patient with normal results. They suggested that the patients with a diagnosis of TGA might be heterogeneous. Two other studies that examined TGA patients [9, 10] attempted and failed to show abnormalities in DWI and apparent diffusion coefficients (ADC).

The findings of our study and previous reports suggest that DWI is useful for the clinical diagnosis of TGA patients. Our case appeared to support the pathophysiology of TGA described by Woolfenden et al. [5]. However, the pathogenesis of the signal alterations and the sensitivity and specificity for the diagnosis are still uncertain. Further clinical studies and advances in neuroimaging technology might establish the usefulness of DWI in the early diagnosis and documentation of the possible heterogeneity of TGA.

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Impact of Subcortical Ischemic Lesions on Behavior and Cognition

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ABSTRACT: **Both cerebrovascular disease and AD are common in the elderly. There are various types of underlying damage to tissue and vessels in vascular cognitive impairment, and the neural mechanisms producing cognitive impairment and the clinical picture are different among the subtypes. Among them, small subcortical infarcts disrupting cortico-subcortical circuits and white matter lesions are the commonest types, and the combination of these two types of lesions might be more realistic than each pure form. Moreover, cognitive impairment of vascular origin may be superimposed on AD. Both vascular and degenerative mechanisms contribute to the development of cognitive impairment, especially in old age, whether they are two independent parallel processes or interacting pathologies. Subcortical small lesions involving the thalamus, caudate, and globus pallidus disrupt cortico-subcortical circuits, resulting in cognitive dysfunction. Disruption of the frontal-subcortical circuits leads to cognitive impairment with striking frontal lobe features, and disruption of the memory-related circuits leads to amnesia. White matter changes, which are certainly related to chronic cerebral ischemia in some patients, are another issue. Patients with dementia and white matter changes may have either AD with cerebrovascular changes or a form of VaD, or a combination of these two etiologies. However, our series of studies have suggested that white matter changes in AD patients are superimposed phenomena of vascular origin and that white matter changes contribute to specific neurological and neuropsychiatric manifestations, but not to global cognitive impairment, which is more closely associated with the degenerative process.**

KEYWORDS: **AD; subcortical; infarcts; circuits; white matter; lesions**

INTRODUCTION

Both cerebrovascular disease and AD are common in the elderly. It is often difficult to determine the impact of each set of lesions on brain function in humans. There are various types of underlying damage to tissue and vessels in vascular cognitive impairment, and the neural mechanisms producing cognitive impairment and the clinical picture are different among the subtypes. Among them, small subcortical infarcts disrupting cortico-subcortical circuits and white matter lesions are the

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commonest types. Moreover, cognitive impairment of vascular origin may be superimposed on AD. Both vascular and degenerative mechanisms contribute to the development of cognitive impairment, especially in old age, whether they are two independent parallel processes or interacting pathologies. Nevertheless, a simplistic approach to the prototypical forms, avoiding confounding interference from concurrent association, may be possible.[1–3]

SMALL SUBCORTICAL INFARCTS DISRUPTING CORTICO-SUBCORTICAL CIRCUITS

Subcortical small infarcts are mostly of lacunar type, but other stroke mechanisms may be involved.[4] Symptom onset may be associated with stroke episodes in some patients and is obscure in others. These lesions disrupt cortico-subcortical circuits, resulting in cognitive dysfunction. Small infarcts involving the thalamus, striatum, and globus pallidus, which are central components of the cortico-subcortical circuits,[5] and those disrupting the neural pathway connecting these structures are classified into strategic lesions.[6] Disruption of the frontal-subcortical circuits leads to cognitive impairment with striking frontal lobe features,[5] and disruption of the memory-related circuits leads to amnesia.[7,8] The issue in evaluating each patient is whether the small lesions are really affecting critical structures. In patients with strategic lesions disrupting the cortico-subcortical circuits, hypometabolism or hypoperfusion may be demonstrated in the relevant cortical area on functional brain imaging, whereas lesions sparing the critical sites and not leading to cognitive impairment may not be associated with such pattern of cortical involvement. Frontal involvement may be a functional brain imaging sign of subcortical strategic lesions leading to cognitive and behavioral impairment. On the contrary, in patients with lesions not leading to cognitive impairment, such cortical involvement is not found on functional brain imaging.

Medial Thalamic Infarcts of Paramedian Thalamic Artery Territory

The paramedian thalamic artery arises from the mesencephalic portion of the posterior cerebral artery and irrigates the medial part of the thalamus. It often sends branches bilaterally, and occlusion of the posterior cerebral artery leads to bilateral thalamic infarction. The syndrome of paramedian thalamic artery territory infarction features sudden onset of coma or confusion followed by an amnesia of varying severity, with or without language impairment and frontal lobe dysfunction. Sometimes, a disinhibition syndrome may be the main feature.[9,10] When the left unilateral thalamus is involved, amnesia is confined to verbal materials.[8]

By using PET, we studied a patient with bilateral paramedian thalamic infarcts who presented with a severe anterograde and retrograde amnesia, hypersomnia, inattention, and personality changes characterized by euphoria, disinhibited behaviors, and childlike speech.[3] High spatial resolution magnetic resonance (MR) images and stereotaxic lesion localization with Shaltenbrand and Wahren's stereotaxic atlas[11] revealed lesions in the internal medullary lamina and dorsomedial, centromedian, and ventral nuclei. A PET demonstrated widespread cerebral hypometabolism, accentuated in the frontotemporal lobes, indicating that the behavioral changes and

amnesia could be attributed to a disruption of the fronto-striato-pallido-thalamic circuits and the amygdala-related Yakovlev circuit, most probably at the internal medullary lamina, and the hypersomnia to damage in the nonspecific thalamic nuclei.

Anterior Thalamic Infarcts of Polar Thalamic Artery Territory

The polar thalamic artery arises from the posterior communicating artery and irrigates the anterior thalamic nuclei and the adjacent nuclei and tracts. A verbal memory loss that is not accompanied by retrograde amnesia and disorientation, and language disturbance characterized by anomia, low verbal fluency, and a difficulty of word definition, which is interpreted as a verbal semantic memory loss, are neuropsychological features of left anterior thalamic infarction. In addition, frontal lobe dysfunction including impairment of executive function, abulia, and either indifference or depression is characteristic. Ghika-Schmid and Bogousslavsky studied 12 patients (8 with a left-sided infarct, 4 with a right-sided infarct) with an isolated anterior thalamic infarct, predominantly in the territory of the polar artery.[12] The clinical features included anterograde memory impairment primarily verbal in left-sided infarcts and visuospatial in right-sided infarcts, perseverative behavior, apathy, dysexecutive syndrome, word-finding difficulties, and anomia. Visual neglect or topographic disorientation was found in 3 patients. Functional recovery was generally good, except for memory dysfunction and apathy. MR images demonstrated involvement of the anterior group of thalamic nuclei, the mamillothalamic tract, and the anterior part of the internal medullary lamina, with structural sparing of the dorsomedial and ventrolateral nuclei.

We studied the neuroimaging features of left polar artery territory infarcts based on 6 patients with infarcts restricted to the left anterior thalamic infarcts of polar artery territory.[13] A lesion analysis with high spatial resolution MR images of each patient and a stereotaxic lesion localization revealed that the common lesion site included the mamillothalamic tract and internal medullary lamina and a part of ventroanterior and ventrolateral nuclei. A study of 15 O-oxygen steady state PET in the patients, in comparison with 6 age/sex-matched healthy subjects by Statistical Parametric Map (SPM96) software, showed a significant reduction in cerebral blood flow and oxygen metabolism in the anterior temporal lobe, including the amygdala, the medial prefrontal cortices, and the anterior cingulate gyrus in the left hemisphere, as well as in the left thalamus. These results suggest that the mamillothalamic tract, which is a part of the hippocampal-related Papez circuit, and the ventral portion of the internal medullary lamina, which contains the ventroamygdalofugal pathway of the amygdala-related Yakovlev circuit, are the most likely candidates for the verbal memory loss. This supports the model of the memory system proposed by Warrington and Weiskrantz[14] and by Mishkin.[15] In addition, disruption of the fronto-striato-pallido-thalamic circuits leads to apathy, abulia, and depression. Functional brain imaging actually demonstrates the disruption of the relevant circuits.

Capsular Infarcts

Tatemichi *et al.* reported 6 patients with an abrupt change in behavior after infarction involving the inferior genu of the internal capsule.[6] The acute syndrome featured fluctuating alertness, inattention, memory loss, apathy, abulia, and psycho-

motor retardation, suggesting frontal lobe dysfunction. Neuropsychological testing in 5 patients with left-sided infarcts revealed severe verbal memory loss. Additional cognitive deficits consistent with dementia were evident in 4 patients. A right-sided infarct caused transient impairment in visuospatial memory. Functional brain imaging in 3 patients showed a focal hypoperfusion most prominent in the ipsilateral inferior and medial frontal cortex and in the medial and lateral temporal cortex.

Important pathways of the limbic system traverse the inferior capsule in the region of the genu. The anterior thalamic peduncle conveys reciprocal connections between the dorsomedial thalamic nucleus and the cingulate gyrus, as well as the prefrontal and orbitofrontal cortices. The inferior thalamic peduncle carries fibers that connect the thalamus with the orbitofrontal, insular, and temporal cortices, as well as the amygdala, via the ansa peduncularis, to the ventral amygdalofugal pathway. Tatemichi *et al.* inferred that the capsular genu infarct interrupted the inferior and anterior thalamic peduncles, resulting in functional deactivation of the ipsilateral frontal and temporal cortex and causing striking frontal behavioral effects and memory loss in their patients.[6] They coined the term "strategic-infarct dementia" for one mechanism for cognitive deterioration from a lacunar infarct that disrupts the thalamo-cortical connection.

Striatal and Pallidal Lesions

Striatal and pallidal lesions lead to behavioral and cognitive changes including abulia, apathy, and depression in some patients[16–18] and disinhibition, hyperactivity, and inattention in others. The changes are often accompanied by abnormalities in executive functions. Episodic memory is generally preserved.

Lesions in the head of the caudate nucleus may cause behavioral changes characterized by apathy, disinhibition, and affective disturbance. In an acute phase, visual and auditory hallucinations are occasionally associated. Neurological abnormality is often missing.[18] We described a patient with bilateral caudate infarcts, who presented with a peculiar behavioral abnormality very similar to frontotemporal dementia including disinhibited and stereotyped behavior, lack of insight, and poor attention.[3] A PET in this patient demonstrated that cerebral blood flow and oxygen metabolism were decreased in the frontal lobes and basal ganglia. These findings suggested that clinical manifestation was caused by a disruption of the lateral orbitofronto-striato-pallido-thalamic circuit, leading to an orbitofrontal syndrome with prominent disinhibition and irritability.[5] Giroud *et al.* reported the features of lenticular infarction in 20 patients.[19] According to their study, behavioral and cognitive disorders were associated with infarcts within the globus pallidus, whereas both motor disorders (dystonia) and cognitive disorders were associated with infarcts within the putamen. In both groups, a frontotemporal hypoperfusion was demonstrated by SPECT.

WHITE MATTER LESIONS

White matter lesions are detected in the otherwise normal brain and in various neurological diseases and strokes. White matter lesions are certainly related to chronic cerebral ischemia in some patients. However, the impact of such lesions on cognitive function is still controversial. In white matter lesions, documenting the

presence of chronic ischemia and then illustrating a functional deprivation of cortices would be the most important role of functional brain imaging. Although a number of functional brain imaging studies have addressed the impact of white matter lesions on cerebral blood flow and metabolism and cognitive function, patients associated with subcortical infarcts are not necessarily excluded.

Direct evidence indicating a close association between chronic ischemia and white matter changes and their relation to dementia has been documented in patients with proven vascular lesions and chronic cerebral ischemia.[20] Cerebral blood flow and energy metabolism measurement with PET in individuals with small arterial diseases and white matter lesions has also demonstrated a state of misery perfusion.[21–24] According to these studies, white matter lesions are caused by chronic cerebral ischemia. Compensated ischemia without oxygen metabolism changes does cause white matter changes, but would not lead to cognitive impairment. In contrast, uncompensated cerebral ischemia with decreased oxygen metabolism, even though uncoupled with the degree of ischemia, would produce severe white matter changes and brain dysfunction. Very severe white matter change, which may disrupt the cortico-cortical and cortico-subcortical connections, may produce cognitive impairment. Alternatively, severe ischemia with disturbed energy metabolism or other factors including degenerative cell loss may be directly involved. The relationships among white matter changes, brain function, and structural changes remain controversial and should be studied further.

Both white matter changes and lacunar infarcts are caused by small-vessel disease.[25,26] Lacunar infarcts are likely to be accompanied by white matter changes. It would be difficult to differentiate the contribution of each lesion on brain function in such cases. Nevertheless, the more lacunar infarcts occur, the more likely the lesions involve the sites critical for cognitive functions. In such cases, subcortical infarcts rather than white matter changes may explain the cognitive decline. Furthermore, factors other than lacunar infarcts and white matter changes, such as degenerative changes, might be involved in brain dysfunction.[27]

VASCULAR LESIONS AND ALZHEIMER'S DISEASE

Both cerebrovascular disease and AD are common in the elderly. Vascular lesions may occur in patients with AD. White matter changes in patients with dementia are causing a big diagnostic dilemma. Patients with dementia and white matter changes may have either AD with cerebrovascular changes or a form of VaD, or a combination of these two etiologies. We should determine the nature of white matter changes and the impact of them on cognitive function and behavior.[28]

In our PET study, 16 probable AD patients with no or minimal evidence of white matter hyperintensity on T2-weighted MR images were compared with 16 age/sex-matched dementia patients who had moderate to severe white matter changes, but no infarct.[29] The patients in the latter group fulfilled the probable AD criteria, except for the white matter changes. The two groups were comparable for demographics, duration of dementia, severity of dementia, and features of dementia. Using PET and the 15 O-oxygen steady state method, blood flow, oxygen metabolism, and oxygen extraction fraction were determined. Cerebral blood flow was significantly lower in patients with white matter changes uniformly over the hemisphere than in those

without white matter changes. Oxygen metabolism was comparable between the two groups. Oxygen extraction fraction was significantly increased in patients with white matter changes equally over the hemisphere. Also, there was a positive correlation of severity of white matter changes with oxygen extraction fraction. These findings suggest that white matter changes are a consequence of latent ischemia, a state of misery perfusion, not only in the deep structures, but also in the whole cerebral cortex. Preservation of oxygen metabolism suggests the absence of clinical correlates. The contribution of white matter changes to the dementia seems negligible. As long as oxygen metabolism is maintained, reduced blood flow has little impact on global cognitive function, despite leading to white matter changes.

In our recent cohort studies, irregular periventricular or confluent deep white matter changes in patients with dementia were significantly associated with hypertension and lacunar infarcts, indicating that white matter changes are of an ischemic origin.[30,31] In a study of patients with dementia either of AD or of subcortical ischemic VaD, or of a combination of these two etiologies, we found that age, hypertension, and lacunar infarcts were independently associated with white matter changes on MRI, indicating an ischemic origin of white matter changes.[30] The frequency of apolipoprotein E ε4 allele in this cohort was as high as in a cohort of AD, irrespective of white matter changes or criteria-based diagnosis of VaD, suggesting that AD is the most likely cause of the dementia. As for the effect of white matter changes on clinical manifestation of dementia, we studied the association between the volume of white matter hyperintensities on T2-weighted images and cognitive, neurological, and neuropsychiatric symptoms, quantifying the volume of white matter hyperintensities and whole brain atrophy.[31] Whole brain atrophy was significantly associated with dementia severity and cognitive disturbances, as well as with grasp

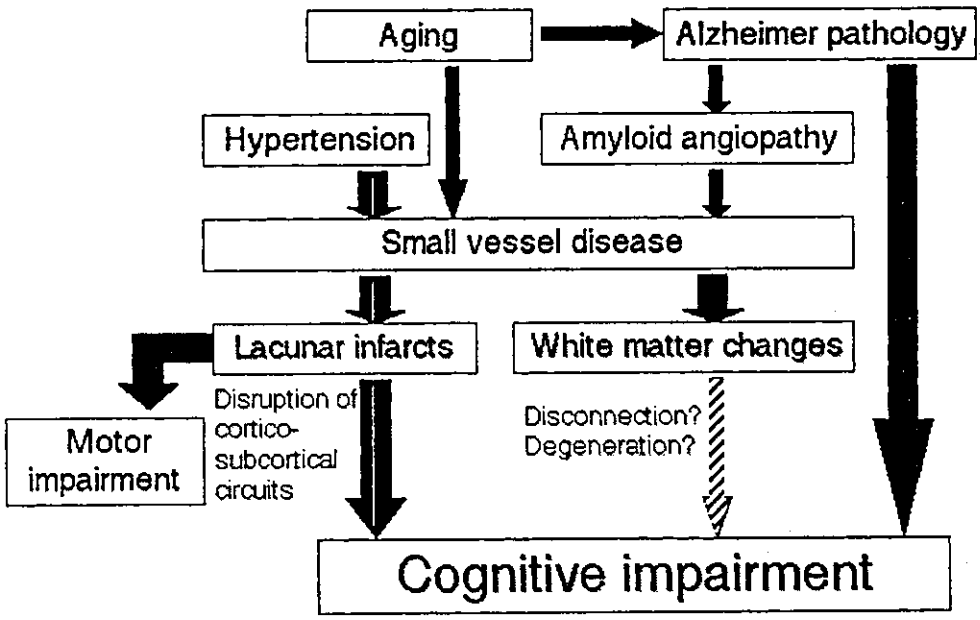

FIGURE 1. Interaction of subcortical ischemic lesions and Alzheimer pathology.

reflex and some kinds of neuropsychiatric disturbances; in contrast, the volume of white matter hyperintensities was not associated with global cognitive disturbances or dementia severity, but was significantly associated with urinary incontinence, grasp reflex, and aberrant motor behaviors.

All these studies have demonstrated that white matter changes in AD patients are superimposed phenomena of vascular origin. White matter changes contribute to specific neurological and neuropsychiatric manifestations, but not to global cognitive impairment, which is more closely associated with brain atrophy, probably due to AD pathology. FIGURE 1 summarizes the concepts of subcortical ischemic lesions producing dementia and of the interaction between vascular lesions and Alzheimer pathology. Although critical sites are rarely affected in isolation, the more lacunar infarcts occur, the more likely they involve the sites critical for cognitive functions. White matter changes, which may disrupt the cortico-cortical and cortico-subcortical connections, may be involved in some of the symptoms, but the contribution would not be dominant. Subcortical infarcts rather than white matter changes explain the cognitive decline. Motor or any other neurological deficits are independent from cognitive impairment. However, the more lacunar infarcts occur, the more they are likely to be associated. Furthermore, degenerative changes might be involved in brain dysfunction.

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特集Q23

脳卒中になると、ぼけるのでしょうか？

A 大脳の特定の部位が障害されると、痴呆や認知障害が起こります。発作を繰り返すほど痴呆を生じやすく、また悪化するので、予防が重要です。

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脳卒中は大脳を冒す

脳卒中は、言葉どおり、脳を冒す疾患です。脳の中でも脳卒中が最も起こりやすい場所は大脳です。大脳は運動や知覚の中枢であり、行動や認識、言語や記憶といったさまざまな認知機能が存在する精神の座です。したがって、そこが損傷されると精神機能も障害されます。

特定の機能は大脳皮質の特定の部位に散らばって存在しています（機能の局在といいます）。冒された部位に従って、そこにあった機能が障害され、後遺症として残ります。例えば、運動中枢が損傷されればまひが残りますが、言語中枢が損傷されれば言語機能の障害（失語症）が残ります。

痴呆もそのような後遺症の一つです。痴呆や認知障害が起こるか否かは、脳のどの部位が損傷されたかによります。

痴呆とは

痴呆とは、一度正常なレベルまで発達した精神機能が、なんらかの脳の障害のために病的に低下した状態のことです。特定の疾患名ではなく、病的な状態を指す医学的な術語です。記憶、見当識（いつ、どこにいるかといった自分のおかれている状況の認識）、注意や集中、計算、言語、道具の使用、学習、思考、判断などの基本的な認知機能のうち、少なくとも2つ以上の機能の障害が痴呆という診断には必要とされています。なかでも記憶障害の存在が最も重視あるいは必須とされています。また社会的・職業的機能に重大な障害をもたらすほどの、あるいは個人的日常生活に支障が生じる程度の認知機能障害を呈して、はじめて痴呆と診断されます。脳卒中はアルツハイマー病とともに、痴呆を起こす重要な原因疾患の一つです。

血管性痴呆

脳血管の狭窄や塞栓による梗塞、あるいは脳血管の破綻に伴う出血が原因で脳が損傷され痴呆に至った状態は、「血管性痴呆」と呼ばれています。脳卒中で認知障害を生じても、痴呆の定義や診断基準に合致しないことも多いので、そのようなものも含めて「血管性認知障害」と