16) Yao H, Sadoshima S, Kuwabara Y, Ichiya Y, Fujishima M : Cerebral blood flow and oxygen metabolism in patients with vascular dementia of the Binswanger type. Stroke 21 : 1694–1699, 1990

Abstract

Distribution of Ischemic Leukoaraiosis in MRI : A Difference from White Matter Lesions in CADASIL

by

Hidekazu Tomimoto*, Ryo Ohtani*, Hideaki Wakita*, Jin-Xi Lin*, Yukio Miki**, Toshiki Mizuno***

from

Departments of *Neurology and **Diagnostic Radiology, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

*** Department of Neurology, Graduate School of Medicine, Kyoto Prefectural University, Kawara-machi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Previously, the distribution of white matter lesions in CADASIL has been reported to be distinct from those in patients with ischemic leukoaraiosis and Binswanger's disease. In earlier European studies, diagnostic significance of white matter lesions in the temporopolar region (Tp), medial frontopolar region (Fp) and external capsule (EC) was stressed in diagnosing CADASIL. More recently, however, high sensitivity and specificity of Tp lesions have been demonstrated. In Japan, prevalence of CADASIL is lower, and those of ischemic leukoaraiosis and Binswanger's disease, likely related to small artery disease, are much higher than in Caucasian countries. Therefore, we examined the frequencies of CADASIL-associated lesions in 17 non-demented patients with ischemic leukoaraiosis and 20 patients with Binswanger's disease. The Binswanger's disease group showed a significantly lower scores for Hasegawa Dementia Rating Scale Revised (HDSR) and a higher prevalence of hypertension, compared to the ischemic leukoaraiosis group. There was only 1 patient with Tp lesions in each group, while Fp lesions were found in 12 % and 50% in the ischemic leukoaraiosis group and Binswanger's disease group, respectively, and EC lesions in 59% and 80%. These results indicated that Tp lesions were useful diagnostic marker in diagnosing CADASIL, whereas Fp and EC lesions were non-specifically observed.

(Received : September 29, 2004)

Acta Neurochir (2005) [Suppl] 95: 183–190

Printed in Austria

Quantitative evaluation of cerebrovascular reactivity in brain tissue by a refill kinetic method of transcranial ultrasonic perfusion imaging: a comparison with Doppler sonography

T. Shiogai[1], A. Morisaka[1], N. Takayasu[2], K. Yoshikawa[2], T. Mizuno[2], M. Nakagawa[2], and H. Furuhata[3]

[1] Department of Clinical Neurosciences, Kyoto Takeda Hospital, Kyoto, Japan
[2] Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto, Japan
[3] Medical Engineering Laboratory, Tokyo Jikei University School of Medicine, Tokyo, Japan

Summary

To confirm the reliability of a refill kinetic method of ultrasonic harmonic perfusion imaging (HPI) capable of quantifying separate parameters of microvascular blood flow velocity and volume in brain tissue, we evaluated acetazolamide (ACZ) cerebrovascular reactivity by transcranial HPI in comparison with Doppler sonography (TCD).

Methods. HPI during continuous Levovist™ infusion with changing pulsing intervals (t) and TCD time-averaged maximum velocity (TAMX) in the middle and posterior cerebral arteries were evaluated before and after ACZ administration in 12 patients, 8 without and 4 with a temporal skull defect. Plateau value (A) and rise rate (β) of intensity (I) represented by HPI time-intensity curves of $I(t) = A(1 - e^{-\beta * t})$ were analyzed on the axial diencephalic plane.

Results. 1) A significantly decreased in proportion to the region of interest location depth only in the intact skull cases. 2) Despite inter- and intra-individual data scattering, in correspondence with TAMX increases after ACZ, significant β increases were more frequently identified than increases of A.

Conclusions. Cerebral vasoreactivity analysis utilizing refill kinetics of transcranial HPI can potentially provide separate quantification based on microvascular blood velocity and volume (capillary patency) with consideration of depth-dependant ultrasound attenuation. This should be suitable for bedside evaluation of neurointensive care patients.

Keywords: Transcranial ultrasonic perfusion imaging; second harmonic imaging; echo-contrast agents; transcranial Doppler sonography; acetazolamide cerebrovascular reactivity; refill kinetics; quantification; skull defects; intact skull.

Introduction

Transcranial ultrasonic harmonic imaging utilizing echo-contrast agents (ECA) has been introduced for repeatable non-invasive bedside measurements of brain tissue perfusion, and has been used in quantitative evaluation utilizing intravenous bolus tracer kinetics [10, 12, 17]. Parameters from time-intensity curve analysis after a bolus ECA injection have been evaluated [4, 6, 10, 12, 17] and correlated with dynamic CT [17] and perfusion MRI [8]. However, quantitative reliability of the transcranial harmonic perfusion imaging (HPI) has not yet been established, mainly due to skull- and depth-dependent attenuation of the ultrasound signals [10, 12, 17]. Furthermore, the dye-dilution principle [7] commonly utilized in neuroradiological perfusion imaging would not be applicable for the bolus kinetics of HPI due to the additional problems of bubble saturation [1] and shadowing effects [13].

To overcome problems of intravenous bolus kinetics, refill kinetics utilizing constant ECA intravenous infusion have been introduced in myocardial echocardiography [20] and have been tested in the quantitative evaluation of brain tissue perfusion in canine subjects with skull defects [11] and with an intact skull [14], and in normal subjects [15]. The refill kinetic method of HPI is able to quantify separate parameters of microvascular blood flow volume (A) and velocity (β) in brain tissue without knowledge of arterial input function [20]. Furthermore, calculated blood flow ($F = A \times \beta$) correlates neatly with cerebral blood flow measured by radiolabeled microsheres [11].

To overcome the problem related to depth-dependent attenuation, we have introduced acetazolamide (ACZ) vasoreactivity tests for quantitative evaluation at the same depth by HPI, and correlated these with transcranial Doppler sonography (TCD) and dynamic CT [18]. The objective of this study is to confirm

Table 1. *Clinical characteristics of patients with an intact skull (IS) and skull defects (SD)*

	IS	SD
n	8	4
Age mean ± SD	75 ± 10	64 ± 11
(range)	(58–85)	(55–79)
Primary diagnosis		
Cerebral infarction		
lacunar	2	0
atherothrombotic	1	0
embolic	3	0
Cerebral hemorrhage	1	2
Subarachnoid hemorrhage	0	2
Alzheimer dementia	1	0
*Major site of lesions**		
R	3	2
L	3	2
Diffuse or none	2	0
Examined side		
R	7	2
L	1	2

* CT, MRI, MRA, and/or Color Duplex Sonography.

the reliability of this method. Therefore, we evaluated ACZ cerebrovascular reactivity in neurological patients by transcranial HPI and compared this with TCD.

Materials and methods

The subjects were 12, mainly stroke patients (aged 55–85 years; mean, 72) with stable clinical conditions in the chronic stage: 8 patients had an intact skull (IS) and 4 patients had craniectomized skull defects (SD) (Table 1). Informed consent was obtained from patients and/or patients' family members.

Utilizing a SONOS 5500 ultrasound system with a S4 ultrabands (1.8/3.6-MHz) transducer (Philips) 124 images, taken by transient response harmonic B-mode imaging, were evaluated during continuous Levovist™ (400 mg/ml) infusion via the antecubital vein, with changing pulsing intervals (t: ms) of: 250, 500, 750, 1000, 1500, 2000, 3000, 4000 (Fig. 1a). The investigation depth was 12 cm with a focus on 6 cm. The mechanical index, system gain, and compression were 1.6, 75 (or 100) and 70, respectively. The images were recorded by T-INT mode and stored on an MO disk. The HPI was evaluated at resting state with 2 infusion rates (0.5 and 1 ml/min.), and 15 minutes (0.5 ml/min.) and 30 minutes (1 ml/min.) after Diamox® 500 mg intravenous injection (Figs. 1 and 2). Time-averaged maximum velocity (TAMX) in the middle and posterior cerebral arteries (MCA and PCA) was measured by TCD just before HPI. The relative changes (%Δ) of TAMX were also evaluated at rest and after ACZ administration (TAMX after ACZ – TAMX at rest/TAMX at rest × 100). Time-intensity curves of HPI were created for 3 regions of interest (ROI) on the axial plane involving the temporal lobe (TL), basal ganglia (BG), and thalamus (Th) via a temporal window (Fig. 1b). Quantification was performed by Acoustic Densitometry [2]. Plateau value (A) and rise rate (β) of intensity (I) represented by a curve of $I(t) = A(1 - e^{-\beta * t})$ and calculated F value (= A × β) were analyzed. The curve-fittings for measured data were analyzed by Kyplot (version 2.0). Utilizing a Student t-test and one-way analysis of variance (ANOVA), statistical significance was set at p values less than 0.05.

Results

a) TCD (Table 2): TAMX both in the MCA and PCA after ACZ significantly increased (except for 30 min. in the MCA) in IS cases and tended to increase in SD cases. These increases (%Δ) in the MCA and PCA were 20–21% and 27–40% in IS cases and 24–30% and 25–37% in SD cases, respectively.

b) HPI (Table 3): 1) In IS cases only, A decreased in proportion to ROI location depth (Fig. 1b) in both infusion rates, and both at rest and after ACZ. The decreases of A were significant at rest during 1 ml/min. infusion. In contrast, in SD cases there was no such tendency of decreases in proportion to ROI location depth. However, A in BG tended to be higher than in TL and Th for both infusion rates and both at rest and after ACZ. Regarding infusion rates, there was no dependency in IS cases, but there was a tendency of increase in SD cases. 2) In terms of β, there was no tendency of decreases proportional to ROI location depth in either IS or SD cases. However, in comparison with A, inter- and intra-individual data scattering of β was so pronounced that it resulted in further data scattering of F. Furthermore, the data scattering was more apparent in SD cases than in IS cases. 3) Increases after ACZ were more frequently identified in β (Fig. 2b), thereby impacting on F, mainly in IS cases. Significant increases were observed only in IS cases of β and F in the Th and β in the BG during 0.5 ml/min. infusion and F in the BG during 1 ml/min. infusion. ACZ effects for A were not apparent, particularly in IS cases.

Discussion

In order to clarify the effects of temporal skull- and depth-dependant ultrasound attenuation, we evaluated parameters derived from the refill kinetics of 3 ROIs (TL, BG, and Th) both in IS and SD cases. As a result, A showed proportional decreases to ROI location depth, particularly in IS cases. The A is the plateau value of the echo-enhancement so that the intensity of echo-enhancement directly depended on the ultrasound attenuation. In contrast, we confirmed the result of a previous study [15] that β did not show attenuation in both IS and SD cases.

In the relationship between infusion rate increase

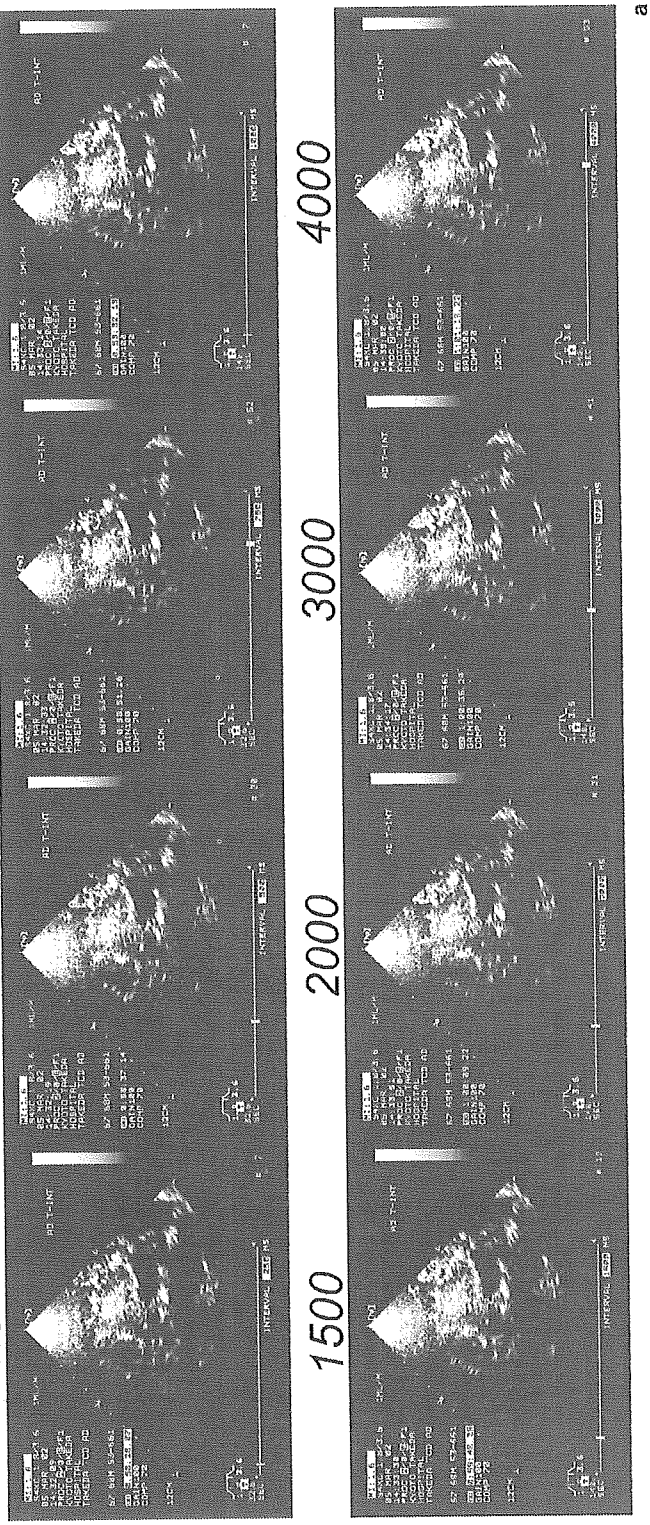


Fig. 1. A 68-year-old IS patient with lacunar infarctions in the Corona Radiata: (a) Serial harmonic perfusion images with increases of pulsing intervals (t) during continuous Levovist™ infusion (1 ml/min)

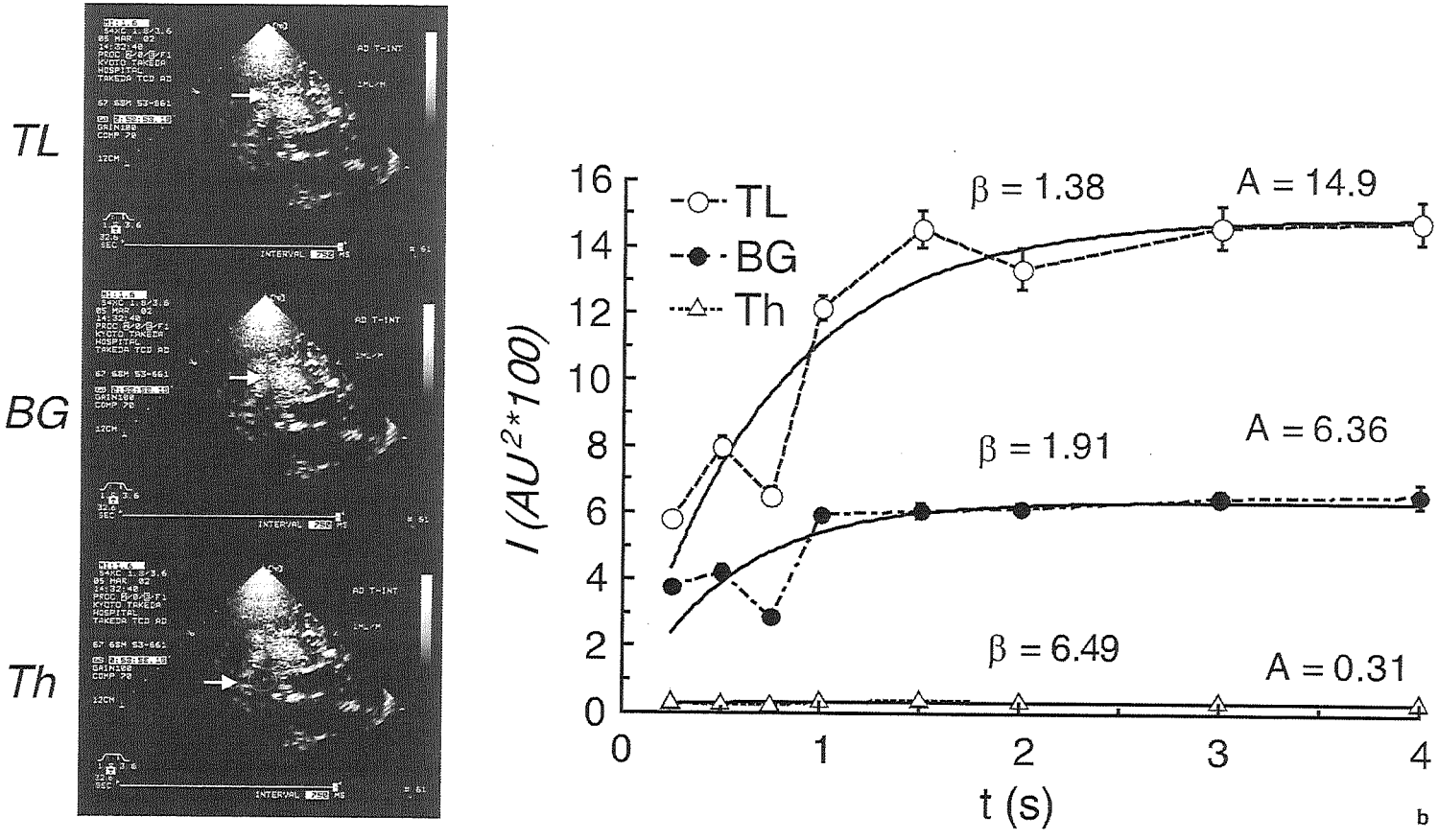


Fig. 1b (*continued*). Data and fitted curves in the 3 regions of interest (*ROI*) placed at the temporal lobe (*TL*), basal ganglia (*BG*), and thalamus (*Th*) (arrows) and are presented in open circles, closed circles, and open triangles, respectively. A and β values were calculated by the t-intensity curves in the 3 ROIs

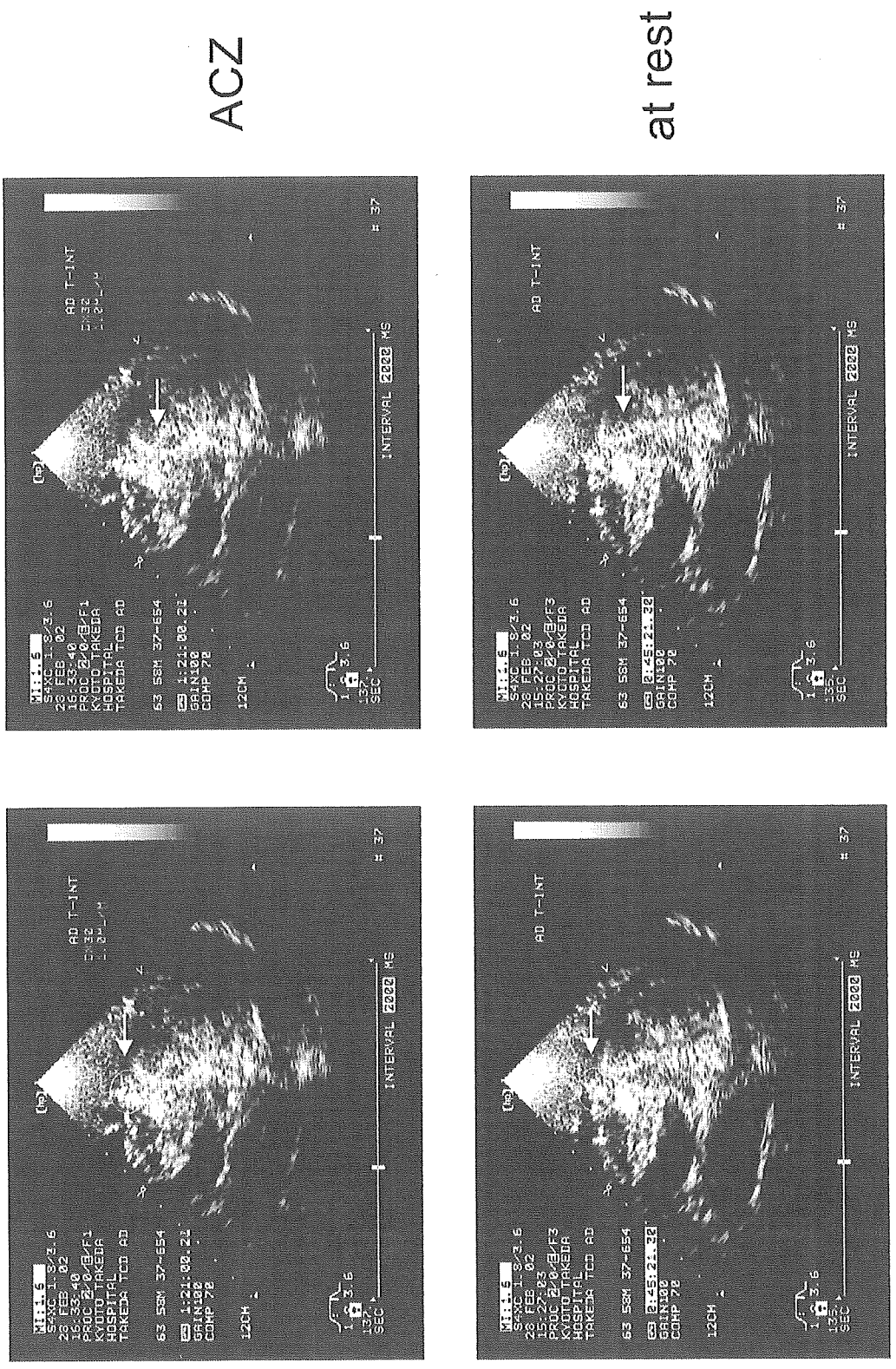


Fig. 2. A 58-year-old IS patient who has a large embolic infarction in the frontal-temporal lobes: (a) Harmonic perfusion images at rest (lower panels) and after ACZ (upper panels). The ROIs at the TL and BG (arrows) are shown in the left and right images, respectively.

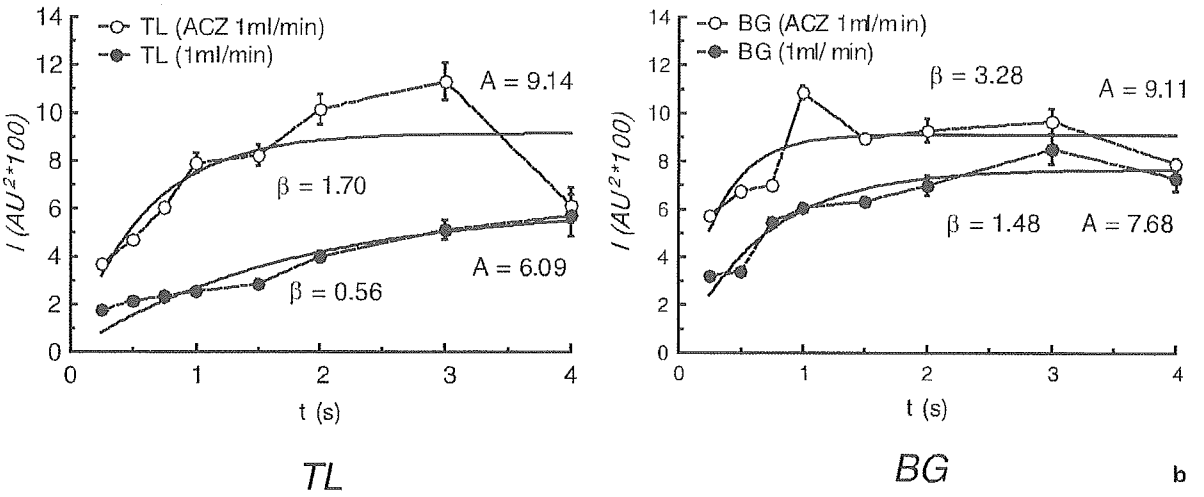


Fig. 2b (*continued*). A and β values were calculated by the t-intensity curves in the left panel of TL and in the right panel of BG. Data and fitted curves were presented at rest (closed circles) and after ACZ (open circles)

Table 2. *TCD Time-averaged Maximum Velocity (TAMX, cm/s) at rest and 15 minutes (ACZ15) and 30 minutes (ACZ30) after acetazolamide administration**

	IS	SD
MCA at rest	48 ± 17	55 ± 11
ACZ15 (%Δ)	59 ± 27† (21 ± 19)	70 ± 4 (30 ± 24)
ACZ30 (%Δ)	56 ± 23 (20 ± 26)	70 ± 7 (24 ± 26)
PCA at rest	28 ± 9	30 ± 5
ACZ15 (%Δ)	38 ± 10‡ (27 ± 16)	41 ± 8 (25 ± 14)
ACZ30 (%Δ)	38 ± 13‡ (40 ± 24)	43 ± 6 (37 ± 27)

* Mean ± SD, † $p < 0.05$, ‡ $p < 0.01$.

and refill kinetic parameters, dependent increases of A and/or F were identified in studies of a myocardial experiment [20] and in a cerebral experiment in normal subjects with an intact skull [14, 15]. However, we identified a tendency of A increases only in SD cases and no dependency in IS cases. This discrepancy in IS cases seems to be caused by skull-dependent ultrasound attenuation in relation to an ECA difference between the first generation of ECA Levovist™ used in our study and second-generation ECA Optison™ in the previous studies [14, 15]. Levovist™, which consists of air with galactose particles and palmitic acids, is necessary mainly to destroy bubbles when creating harmonic perfusion images and, therefore, is more suitable for SD cases [19] than IS cases. Optison™, which consists of a perfuluoropropane gas with albumin solution, is able to produce harmonic signals which come from resonant or oscillating phenomena produced by relatively low acoustic pressure and, therefore, is more suitable for images of microcircula-

Table 3. *HPI findings at rest and 15 minutes (ACZ15) and 30 minutes (ACZ30) after acetazolamide administration**

	IS				SD			
	0.5 ml/min.		1 ml/min.		0.5 ml/min.		1 ml/min.	
	at rest	ACZ 15	at rest	ACZ 30	at rest	ACZ 15	at rest	ACZ 30
A TL	6.38 ± 3.76	7.58 ± 3.60	6.33 ± 1.80†	7.59 ± 3.83	4.07 ± 2.81	4.10 ± 1.29	7.96 ± 4.53	12.2 ± 5.67
BG	3.08 ± 1.11	2.58 ± 0.96	3.18 ± 0.96†	3.23 ± 1.36	15.5 ± 6.29	35.0 ± 21.8	52.8 ± 38.2	39.9 ± 27.6
Th	0.80 ± 0.37	1.13 ± 0.40	1.31 ± 0.70†	0.97 ± 0.48	8.05 ± 5.72	6.98 ± 3.17	21.6 ± 13.7	24.7 ± 12.1
β TL	16.0 ± 7.12	20.1 ± 8.97	7.62 ± 6.22	18.8 ± 7.90	32.8 ± 10.6	26.9 ± 13.6	15.2 ± 12.4	21.5 ± 19.8
BG	19.6 ± 7.14	37.8 ± 6.44§	3.23 ± 1.10	13.8 ± 7.15	29.1 ± 15.4	27.6 ± 11.9	16.8 ± 12.2	38.6 ± 34.5
Th	15.6 ± 5.52	36.1 ± 5.92§	19.4 ± 6.90	14.1 ± 5.33	50.4 ± 7.53	17.8 ± 12.4	27.5 ± 15.7	25.3 ± 20.0
F TL	36.5 ± 23.1	103 ± 79.5	52.6 ± 42.4	51.0 ± 29.1	188 ± 159	109 ± 52.2	86.7 ± 70.4	277 ± 272
BG	45.9 ± 17.3	118 ± 52.0	10.5 ± 4.41	26.8 ± 10.8§	485 ± 321	289 ± 114	224 ± 76.3	2549 ± 2533
Th	4.64 ± 1.39	49.0 ± 20.1§	16.0 ± 8.06	11.3 ± 5.77	517 ± 397	228 ± 201	445 ± 413	565 ± 552

* *TL* temporal lobe, *BG* basal ganglia, *Th* thalamus; mean ± SE, † $p < 0.05$ (ANOVA), § $p < 0.05$ (Student t-test).

tion [16], and would probably be advantageous in IS cases. As a previous study [14] indicated, we confirmed no dependence of infusion rates on β in either IS or SD cases.

In relation to TCD TAMX increases after ACZ, significant increases of β were more frequently identified than those of F in only IS cases. The ACZ effects for A were not always apparent in both IS and SD cases. An experimental study in IS cases showed higher increases of F compared to β after ACZ [14]. In another study involving craniectomized dogs during hyper- and hypo-ventilation, changes of A were more significant than β and F [11]. Several factors probably affect these discrepancies of vasoreactivity on the basis of A, β, and $F = A \times \beta$, e.g. pathological differences, ROI size involving gray and/or white matter, presence of temporal bone, temporal bone structure and thickness, $PaCO_2$, ACZ dose, and time after ACZ etc.

Ultimately, ACZ vasoreactivity utilizing refill kinetics is able to evaluate capillary patency by A increase, and flow velocity in the microcirculation by β increase [5], separately. Our results on the basis of ACZ vasoreactivity in mainly ischemic stroke patients indicated that cerebral capillary patency is more disturbed than microvascular velocity in the pathological brain tissue.

Inter- and intra-individual data scattering of parameters, particularly β impacting on F, were probably due to probe holdings during data acquisition (less than 3 minutes in this study), dynamic range between harmonic B-mode in our study and integrated backscatter in previous studies [14, 15], inhomogeneous insonation conditions in relation to inter-individual difference of temporal bone windows [14, 15] and skull defect size, and so on. Recently, to overcome the problems of refill kinetics, diminution [9] and depletion [3] kinetics have been introduced; however, further studies are essential for complete quantitative measurements of brain tissue perfusion. In conclusion, cerebral vasoreactivity analysis utilizing refill kinetics of transcranial HPI can potentially provide separate quantification based on microvascular flow velocity as β and volume (capillary patency) as A in the brain with consideration of depth-dependant ultrasound attenuation. In particular, β is suitable as a marker of vasoreactivity disturbance in ischemic brain tissue and advantageous for independence of depth and infusion rates. This would be suitable in bedside evaluations of neurointensive care patients with ischemic brain injuries.

References

1. Claassen L, Seidel G, Algermissen C (2001) Quantification of flow rates using harmonic grey-scale imaging and an ultrasound contrast agent: an in vitro and in vivo study. Ultrasound Med Biol 27: 83–88
2. D'Sa A (1999) Acoustic densitometry, Hewlett-Packard Company, USA
3. Eyding J, Wilkening W, Reckhardt M, Schmid G, Meves S, Ermert H, Przuntek H, Postert T (2003) Contrast burst depletion imaging (CODIM): a new imaging procedure and analysis method for semiquantitative ultrasonic perfusion imaging. Stroke 34: 77–83
4. Eyding J, Krogias C, Wilkening W, Meves S, Ermert H, Postert T (2003) Parameters of cerebral perfusion in phase-inversion harmonic imaging (PIHI) ultrasound examinations. Ultrasound Med Biol 29: 1379–1385
5. Frankel HM, Garcia E, Malik F, Weiss JK, Weiss HR (1992) Effect of acetazolamide on cerebral blood flow and capillary patency. J Appl Physiol 73: 1756–1761
6. Harrer JU, Klotzsch C (2002) Second harmonic imaging of the human brain: the practicability of coronal insonation planes and alternative perfusion parameters. Stroke 33: 1530–1535
7. Meier P, Zierler LK (1954) On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 6: 731–744
8. Meves SH, Wilkening W, Thies T, Eyding J, Holscher T, Finger M, Schmid G, Ermert H, Postert T (2002) Comparison between echo contrast agent-specific imaging modes and perfusion-weighted magnetic resonance imaging for the assessment of brain perfusion. Stroke 33: 2433–2437
9. Meyer K, Seidel G (2002) Transcranial contrast diminution imaging of the human brain: a pilot study in healthy volunteers. Ultrasound Med Biol 28: 1433–1437
10. Postert T, Muhs A, Meves S, Federlein J, Przuntek H, Buttner T (1998) Transient response harmonic imaging: an ultrasound technique related to brain perfusion. Stroke 29: 1901–1907
11. Rim SJ, Leong-Poi H, Lindner JR, Couture D, Ellegala D, Mason H, Durieux M, Kassel NF, Kaul S (2001) Quantification of cerebral perfusion with "Real-Time" contrast-enhanced ultrasound. Circulation 104: 2582–2587
12. Seidel G, Algermissen C, Christoph A, Claassen L, Vidal-Langwasser M, Katzer T (2000) Harmonic imaging of the human brain. Visualization of brain perfusion with ultrasound. Stroke 31: 151–154
13. Seidel G, Meyer K, Algermissen C, Broillet A (2001) Harmonic imaging of the brain parenchyma using a perfluorobutane-containing ultrasound contrast agent. Ultrasound Med Biol 27: 915–918
14. Seidel G, Claassen L, Meyer K, Vidal-Langwasser M (2001) Evaluation of blood flow in the cerebral microcirculation: analysis of the refill kinetics during ultrasound contrast agent infusion. Ultrasound Med Biol 27: 1059–1064
15. Seidel G, Meyer K, Metzler V, Toth D, Vida-Langwasser M, Aach T (2002) Human cerebral perfusion analysis with ultrasound contrast agent constant infusion: a pilot study on healthy volunteers. Ultrasound Med Biol 28: 183–189
16. Seidel G, Meyer K (2002) Impact of ultrasound contrast agents in cerebrovascular diagnostics. Eur J Ultrasound 16: 81–90
17. Shiogai T, Tsunezuka C, Ohara T, Imai K, Makino M, Nakajima K, Furuhata (2001) Clinical significance of transcranial contrast-enhanced harmonic perfusion imaging (HPI) as a quantitative method of measuring cerebral blood flow. Neurotraumatology 24: 77–82 (In Japanese)

18. Shiogai T, Koshimura M, Murata Y, Nomura H, Doi A, Makino M, Mizuno T, Nakajima K, Furuhata H (2003) Acetazolamide vasoreactivity evaluated by transcranial harmonic perfusion imaging: relationship with transcranial Doppler sonography and dynamic CT. Acta Neurochir [Suppl] 86: 57–62
19. Shiogai T, Takayasu N, Mizuno T, Nakagawa M, Furuhata H (2004) Comparison of transcranial brain tissue perfusion images between ultraharmonic, second harmonic, and power harmonic imaging. Stroke 35: 687–693
20. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S (1998) Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 97: 473–483

Correspondence: Toshiyuki Shiogai, Department of Clinical Neurosciences, Kyoto Takeda Hospital, Minamikinuta-cho 11, Nishinanajo, Shimogyo-ku, Kyoto 600-8884, Japan. e-mail: shiogait@pop11.odn.ne.jp

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2006;21:162–169
DOI: 10.1159/000090677

Accepted: September 28, 2005
Published online: January 2, 2006

Small Artery Dementia in Japan: Radiological Differences between CADASIL, Leukoaraiosis and Binswanger's Disease

Hidekazu Tomimoto[a] Ryo Ohtani[a] Hideaki Wakita[a] Jin-Xi Lin[a]
Masafumi Ihara[a] Yukio Miki[b] Fumiko Oshima[c] Takaho Murata[d]
Kenichi Ishibashi[e] Toshihiko Suenaga[f] Toshiki Mizuno[g]

Departments of [a]Neurology and [b]Diagnostic Radiology, Graduate School of Medicine, Kyoto University, Sakyo, [c]Department of Neurosurgery, Murata Hospital, Ikuno, Osaka, [d]Department of Neurology, Kyoto 1st Red Cross Hospital, Higashiyama, Kyoto, [e]Department of Neurosurgery, Graduate School of Medicine, Osaka City University, Abeno, [f]Department of Neurology, Tenri Hospital, Tenri, and [g]Department of Neurology, Graduate School of Medicine, Kyoto Prefectural University, Kamigyo, Kyoto, Japan

Key Words
CADASIL · Leukoaraiosis · Binswanger's disease · White matter disorders

Abstract
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary small artery disease which is phenotypically similar to Binswanger's disease (BD), a nonhereditary form of small artery disease. Recent studies have indicated that lesions in the temporopolar, medial frontopolar areas and external capsule are frequently seen in Caucasian patients with CADASIL. However, it remains unclear whether magnetic resonance (MR) imaging findings are helpful in diagnosing small artery disease outside countries with Caucasian populations, since CADASIL is rare despite the high prevalence of small artery disease in Japan. We examined 58 patients with small artery disease, all of whom were devoid of major vessel occlusion or severe stenosis. These patients included 7 patients from 3 families with CADASIL, 27 nondemented patients with extensive leukoaraiosis (LA) and 24 patients with BD. On T_2-weighted MR images, hyperintensities in the temporopolar areas were observed in all 7 patients with CADASIL, whereas these lesions were observed in only 1 subject from each of the nondemented LA and BD groups. Hyperintensities in the medial frontopolar areas were seen in 4 of the 7 patients with CADASIL (57%) and in 14 of the 24 patients with BD (58%), and were more frequent than in the nondemented LA group (4 of the 27 patients; 15%). In contrast, hyperintensities in the external capsule were frequently observed in all groups. Therefore, temporopolar lesions can also serve as diagnostic markers for CADASIL in non-Caucasian patients.

Introduction

Vascular dementia is a heterogeneous syndrome resulting either from large vessel occlusive disease or small artery disease, which consists of lacunar infarctions and leukoaraiosis (LA). In Japan, patients with vascular dementia are more prevalent than in countries with Caucasian populations [1, 2]. In a community-based epidemiological study, vascular dementia represented 40% of all

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/06/0213–0162$23.50/0

Accessible online at:
www.karger.com/dem

Dr. H. Tomimoto
Department of Neurology, Graduate School of Medicine, Kyoto University
54 Shogoin, Kawahara-cho, Sakyo-ku
Kyoto 606-5807 (Japan)
Tel. +81 75 751 3766, Fax +81 75 751 3769, E-Mail tomimoto@kuhp.kyoto-u.ac.jp

Table 1. Demographic variables of the patients

	CADASIL	Nondemented LA	Nondemented LA with parkinsonism[1]	BD
Number of patients	7	27	5	24
Gender, male	2	9	2	13
Mean age, years	58 ± 11[a]	75 ± 6	74 ± 5	73 ± 7
MMSE, mean ± SD	24.7 ± 4.7	25.6 ± 3.1	25.3 ± 6.2	13.8 ± 5.6[a]
CDR	0.4 ± 0.4	0.1 ± 0.2	0.2 ± 0.3	1.2 ± 0.6[b]
Hypertension, yes	2	17	3	22[c]
Diabetes mellitus, yes	1	3	1	4
Hyperlipidemia, yes	1	14	2	6
Smoking, yes	0	9	2	10
Alcohol, yes	0	9	2	11
History of stroke, yes	6	10	0	11

CDR = Clinical Dementia Rating. [a] $p < 0.0001$ versus the other two groups by the Mann-Whitney U test; [b] $p < 0.001$ versus the CADASIL group and $p < 0.0001$ versus the nondemented LA group by the Mann-Whitney U test; [c] $p < 0.001$ versus the CADASIL group and $p < 0.05$ versus the nondemented LA group by the χ^2 test.
[1] Out of the whole nondemented LA group.

dementia cases in Japan [3]. This situation is quite different from the relatively low frequency of vascular dementia in countries with Caucasian populations, in which only 12% of all dementia cases were vascular in a similar community-based study in Rochester, Minn. [4]. Another characteristic feature of vascular dementia in Japan is the high proportion of small artery involvement, constituting 56% of the vascular dementia cases [2].

Small artery disease may cause vascular dementia in patients with multiple lacunar infarctions, LA and Binswanger's disease (BD) but alternatively may emerge as a hereditary form of small artery disease, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). CADASIL is rare in Japan, with less than 20 reported families. In contrast, BD, which is characterized by extensive LA and lacunar infarctions in the basal ganglia and white matter [5], is frequently observed. Patients with BD may show dementia and parkinsonism, and sometimes develop these symptoms without exhibiting any lacunar syndromes or stroke-like episodes. LA is often observed in subjects without dementia [6] and is associated with increased cardiovascular risk factors as well as a future risk of stroke and dementia [7].

CADASIL is diagnosed based on the presence of *Notch 3* mutations or granular osmiophilic material in the skin and cerebral small vessels as revealed by electron microscopy [8]. Using magnetic resonance (MR) scans of CADASIL brains, O'Sullivan et al. [9] reported the diagnostic significance of temporopolar and external capsular lesions. However, more recently, temporopolar and medial frontopolar lesions were shown to be specific in CADASIL, but not the external capsular lesions [10]. It remains unclear whether these diagnostic markers are applicable to non-Caucasian patients, since there is a large variance in the frequency of nonhereditary small artery dementia [1, 2] and *Notch 3* mutations in CADASIL-like patients between countries with Caucasian populations and Japan [11]. Therefore, we tested the validity of these diagnostic markers for CADASIL in Japanese patients with small artery disease.

Patients and Methods

Patients

The study population consisted of 58 patients who visited our institutes or affiliated hospitals from April 1995 to March 2003 (table 1). All patients were assigned to this study consecutively. Those patients with occlusion or severe stenosis of the major cerebral vessels were excluded from the present population based on their brain MR or conventional angiography and carotid ultrasonography. The study population included 7 patients with CADASIL (2 men, 5 women; age range, 38–71 years; mean, 58 years), 27 nondemented patients with LA (9 men, 18 women; age range, 59–83 years; mean, 76 years) and 24 patients with BD (13 men, 11 women; age range, 54–86 years; mean, 73 years). The inclusion criteria for the nondemented LA group were based on normal results from a Mini Mental State Examination (MMSE) score (23<) and a Clinical Dementia Rating scale less than 1. None of the subjects in the nondemented LA group had specific metabolic disorders due to genetic or nongenetic causes nor dementia, but all of them showed grade 3 hyperintensities on T_2-weighted MR images

according to the method of Fazekas et al. [12], regardless of the number of lacunar infarctions. The diagnosis of BD was based on the clinical diagnostic criteria proposed by Bennett et al. [13]. Briefly, all of the patients had dementia, diffuse hyperintensities (grade 3) and at least 2 of the following 3 clinical findings: (a) vascular risk factors or evidence of systemic vascular disease; (b) evidence of focal cerebrovascular disease; (c) evidence of 'subcortical' cerebral dysfunction such as gait disorders, parkinsonism or incontinence.

MR Imaging

The MR examinations were performed with a 1.5-tesla (Signa Advantage; GE Medical Systems, Milwaukee, Wisc., USA) MR unit. In all patients, axial intermediate-weighted fast spin echo (3,400–4,600 ms repetition time/17–20 ms effective echo time) and T_2-weighted fast spin echo images (3,400–4,600 ms repetition time/102–120 ms effective echo time) were acquired. These images were obtained with a 22- to 24-cm-square field of view, a 6- to 8-mm section thickness with a 0- to 2-mm intersection gap, and a 192–256 × 256–320 matrix. The number of excitations was 1 or 2. The echo train length was 8.

Patients with extensive LA were scored according to the Fazekas rating scale by two experienced neurologists (H.T. and R.O.). Hyperintensities in the deep white matter at the level of the centrum semiovale were graded using the following 4-point scale: 0 = no hyperintensities present; 1 = punctate; 2 = early confluent; 3 = confluent lesions. Lesions in the temporopolar and medial frontopolar areas were assessed in a similar manner, but exclusively in the localized region in close proximity to the cerebral cortices. Periventricular hyperintensities at the level of the frontal horn were graded according to the following 4-point scale: 0 = no lesions present; 1 = caps and pencil-thin lining; 2 = smooth halo; 3 = irregular hyperintensities extending into the deep white matter. The hyperintensities in the external capsule were graded as 0 if they were absent, 1 if their length was shorter than one fourth of the external capsule, 2 if it was between one fourth and a half, and 3 if it was longer than one half.

Statistical Analysis

The statistical significance of the intergroup differences was assessed by the χ^2 test for categorical variables and by the Mann-Whitney U test for continuous variables using Statview 5.0 (Abacus Concepts Inc., USA) for a Macintosh computer. A p value <0.05 was considered to be statistically significant.

Results

Demographic Variables

The CADASIL patients were significantly younger than the patients from the other 2 groups, whereas there were no significant differences in age between the nondemented LA and BD groups (table 1). Hypertension was more frequent in the BD group than in the CADASIL and nondemented LA groups. Although 6 out of the 7 CADASIL patients had a history of stroke, they rarely had common risk factors for stroke such as hypertension, hyperlipidemia, smoking or the overconsumption of alcoholic beverages.

Clinical Features of Japanese CADASIL Patients

The diagnosis of CADASIL was based on the presence of autosomal dominant hereditary leukoencephalopathy and lacunar infarction. The proband of family 1 (fig. 1) is presented as follows. A 38-year-old woman was admitted because of numbness in her left leg in October 1999. She had remitting episodes of throbbing headaches and had had a diagnosis of migraines since 1982. Her mother (68 years old), older sister (42 years old) and niece (14 years old) also suffered from migraines. A neurological examination showed no abnormalities, and neuropsychological testing detected normal cognitive function with an MMSE score of 25/30 and a WAIS IQ of 110. Her systolic blood pressure ranged between 110 and 130 mm Hg. Electrophysiological studies revealed peripheral neuropathy. Her older sister had normal cognitive function with an MMSE score of 30 and a WAIS IQ of 120. Her mother had an MMSE score of 25 and a WAIS IQ of 87, and 4 years later suffered a stroke episode and finally exhibited dementia. A genetic analysis of the mother revealed a missense mutation of P167S in exon 4 of the *Notch 3* gene.

In family 2 (fig. 1), 5 out of 6 siblings suffered from cerebrovascular disease. The proband of this family visited our hospital because of dysesthesia in the left upper and lower limbs 15 years ago. CT and conventional cerebral angiography disclosed no remarkable changes. At 59 years old, he complained of diplopia, and a neurological examination showed left medial longitudinal fasciculus syndrome. His 56-year-old sister complained of dysarthria, and a 49-year-old sister suffered from a left sensory disturbance. The analysis of the *Notch 3* gene in these siblings revealed a missense mutation of R141C in exon 4.

In family 3 (fig. 1), the patient had a history of lacunar infarctions and right thalamic hemorrhage at 64 years old. She had hypertension and diabetes mellitus, and was admitted because of seizures at 71 years old. A neurological examination revealed pseudobulbar palsy, parkinsonism and dementia. A genetic analysis revealed a missense mutation of A75P in exon 3 of the *Notch 3* gene.

MR Findings

In the MR scans from CADASIL patients, the proband in family 1 (photo not shown) and her older sister (fig. 2a–c) showed diffuse leukoencephalopathy in the periventricular region, the centrum semiovale, the temporopolar area and the external capsule. Her mother had leukoencephalopathy in a similar region, plus medial frontopolar lesions (fig. 2d–f).

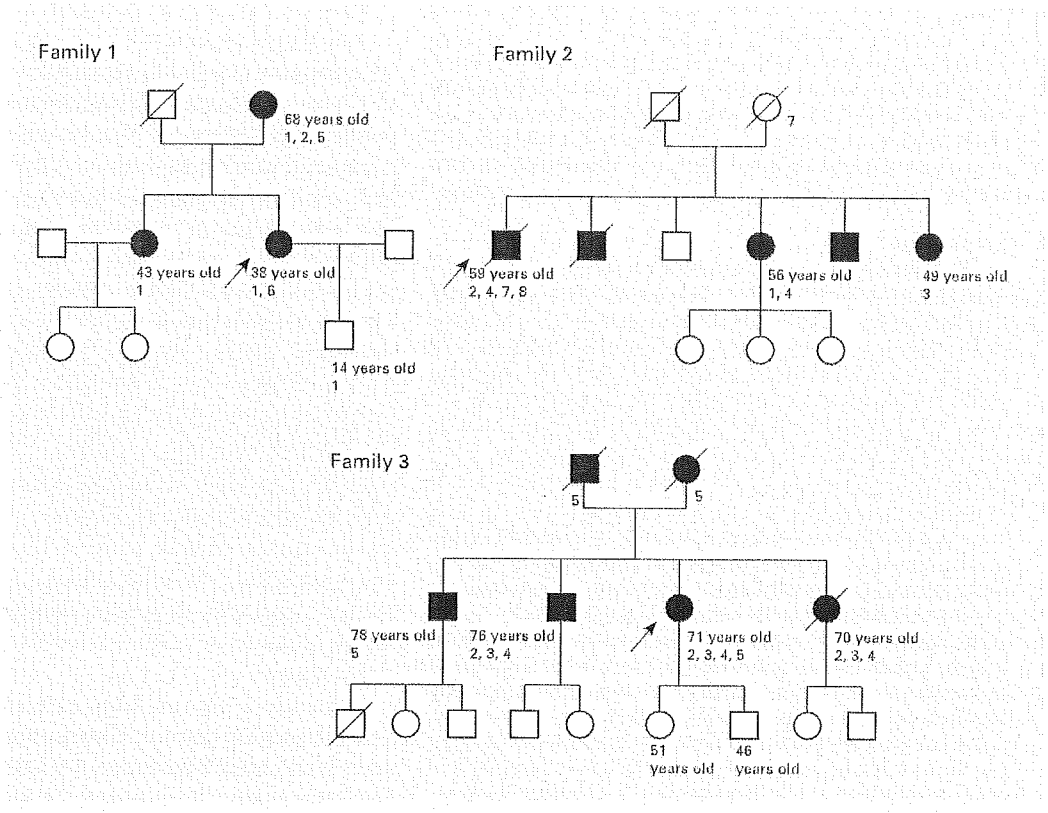


Fig. 1. Pedigrees of families 1, 2 and 3. The numbers indicate the following: 1 = migraine; 2 = hemiplegia; 3 = sensory disturbance; 4 = dysarthria; 5 = dementia; 6 = retinal degeneration; 7 = parkinsonism; 8 = medial longitudinal fasciculus syndrome. The arrows indicate the proband of each family.

Among the 5 persons affected from family 2, 3 were examined. The MR scans of the proband from family 2 showed hyperintensities in the periventricular region, centrum semiovale, medial frontopolar and temporopolar areas and the external capsule (fig. 2g–i), and a frank infarction in the midbrain tegmentum. Further MR scans revealed hyperintensities in the periventricular regions, centrum semiovale and temporopolar area in his 56-year-old sister and similar lesions in the same region plus the external capsule in his 49-year-old sibling (photo not shown). In family 3, the proband showed hyperintensities in the periventricular region, centrum semiovale, medial frontopolar and temporopolar areas and the external capsule (photo not shown). The younger daughter (46 years old) showed no neurological or MR abnormalities. The other members from this family could not be examined.

In the nondemented LA group, hyperintensities were frequently present in the external capsule. Medial frontopolar lesions were infrequent, and temporopolar lesions were absent except for 1 patient. In the BD group, there was 1 patient who had marked hyperintensities in the temporopolar and medial frontopolar regions and the external capsule (fig. 3a–c). However, in most BD patients, these temporopolar lesions were absent (fig. 3d–f).

Semiquantitative Evaluation of Distribution of LA

To evaluate the presence of LA in each region of the white matter, we judged the patient as having significant lesions if he had grade 2 or 3 lesions on at least one side. Only 1 patient showed temporopolar lesions in each of the nondemented LA and BD groups, respectively, but these lesions were invariably observed in all 7 patients with CADASIL. In contrast, medial frontopolar lesions were found in 4 of the 27 patients in the nondemented LA group (15%) and in 14 of the 24 patients in the BD group (58%), which was not significantly different from

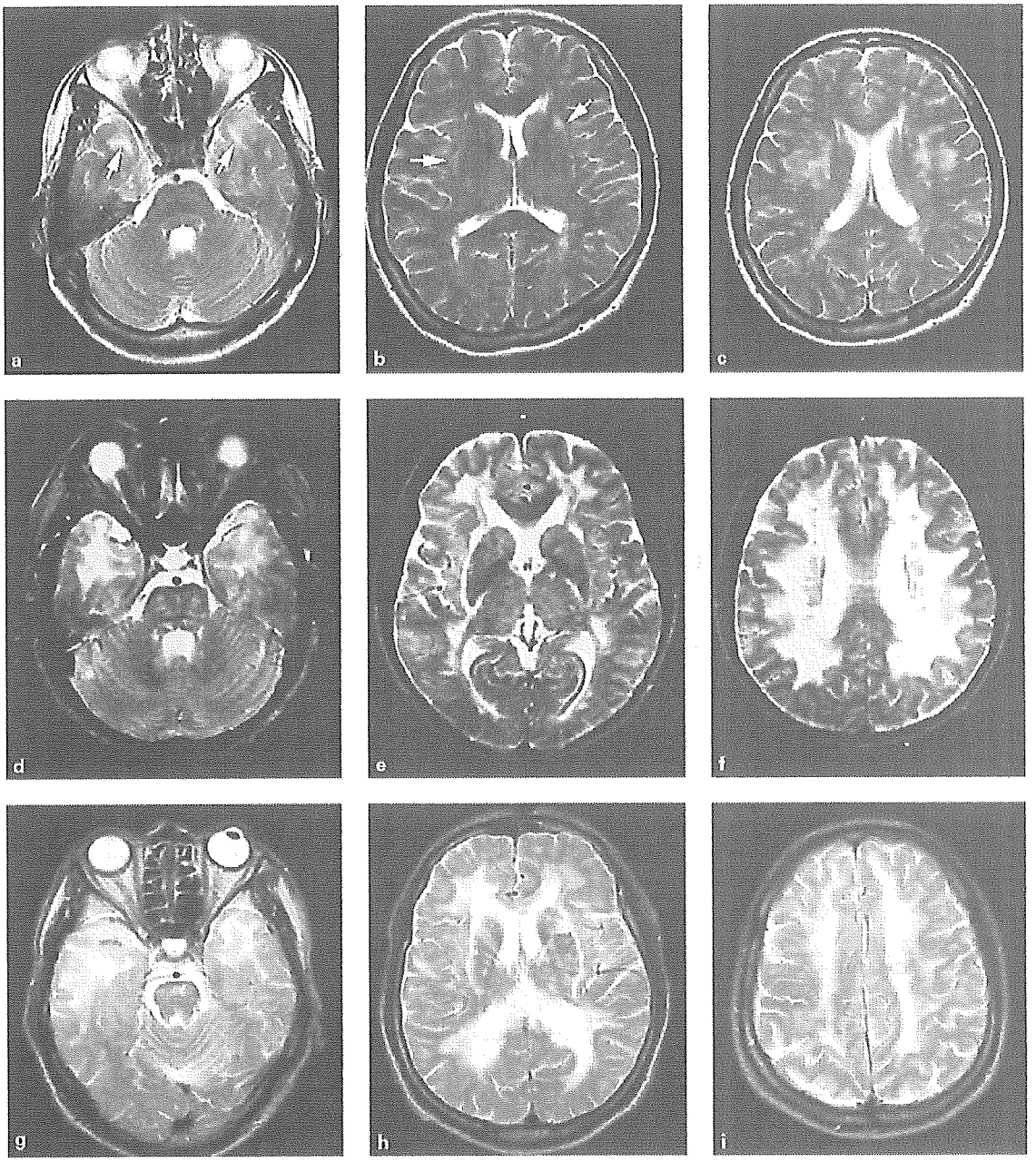


Fig. 2. T_2-weighted MR images of CADASIL patients. **a–c** A 42-year-old female, the older sister of the proband in family 1, showed hyperintense lesions in the temporopolar regions and external capsules (arrows) bilaterally, but not in the medial frontopolar regions. **d–f** Her mother at 68 years old had extensive hyperintensities in all of these regions. **g–i** Similar lesions were observed in a sibling (56-year-old female) of the proband in family 2.

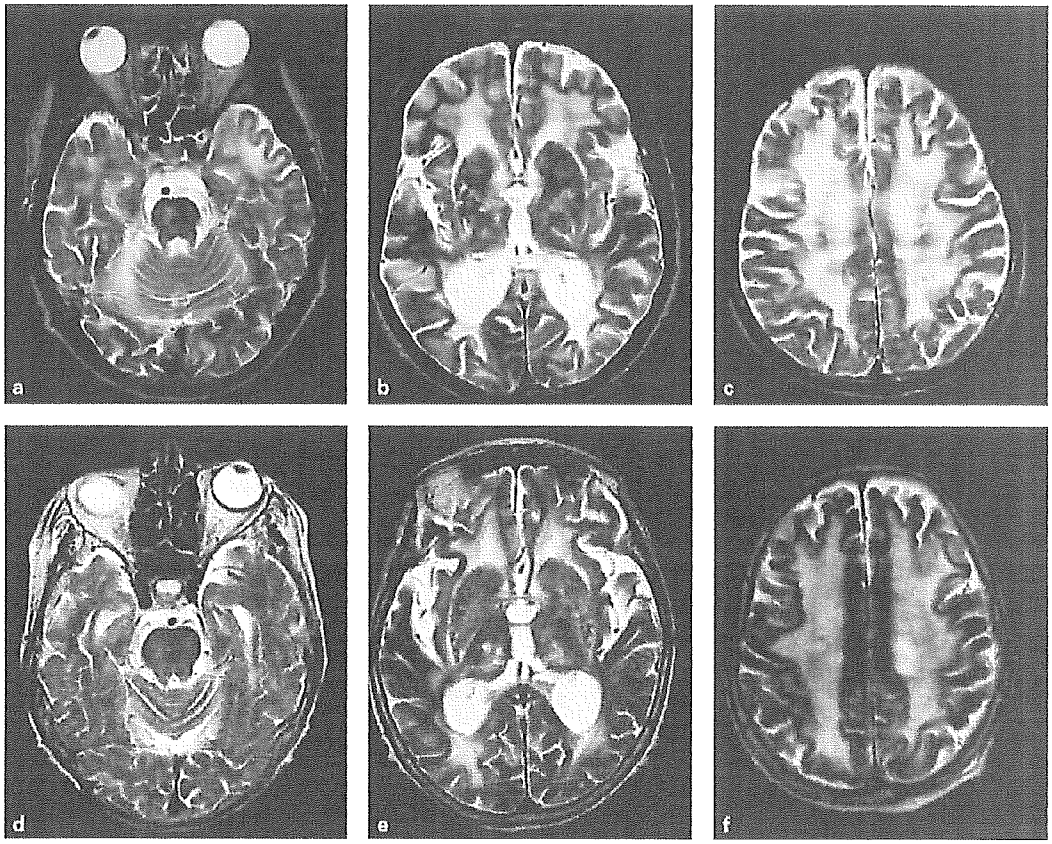


Fig. 3. T_2-weighted MR images of BD patients. **a–c** Only 1 patient (70-year-old male) showed a temporopolar lesion among the 24 patients with BD. **d–f** For comparison, a typical distribution of hyperintensities is shown in the external capsule and medial frontopolar regions, but not in the temporopolar area (77-year-old female).

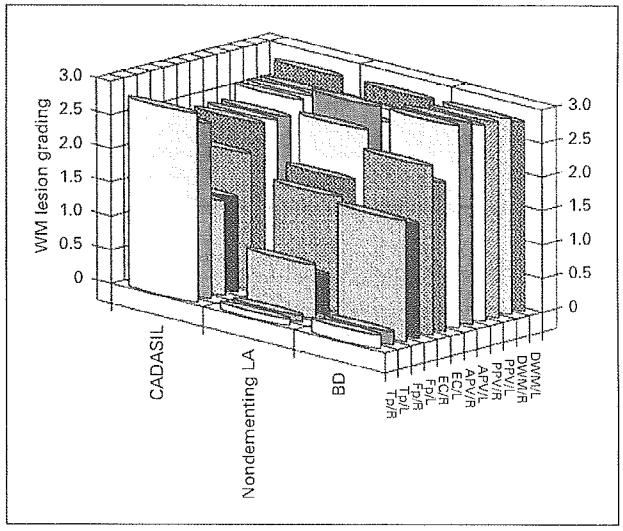


Fig. 4. Grading scores for the white matter (WM) lesions in patients with CADASIL, nondemented LA and BD. Note the marked difference in the frequencies of bilateral temporopolar lesions between the CADASIL group and the other 2 groups ($p < 0.001$ by Mann-Whitney U test). DWM = Deep white matter; L = left; R = right; PPV = post periventricular; APV = ant. periventricular; EC = external capsule; Fp = frontopolar; Tp = temporopolar.

the prevalence in 4 of the 7 patients with CADASIL (57%). Lesions in the external capsule were present in 6 of the 7 patients with CADASIL (86%) and were also observed in 18 of the 27 nondemented patients with LA (67%) and in 19 of the 24 patients with BD (79%).

Figure 4 shows the results of the average grading scores in each area. The grading scores in the temporopolar area were significantly higher in the CADASIL group (2.8 ± 0.4 on the right, 2.6 ± 0.5 on the left) than in the other two groups (0.1 ± 0.4 on the right, 0.1 ± 0.6 on the left for the non-demented LA group; 0.2 ± 0.8 on the right, 0.2 ± 0.7 on the left for the BD group; $p < 0.001$). The grading scores in the medial frontopolar area were higher in the BD group (1.8 ± 1.2 on the right, 1.7 ± 1.2 on the left) than in the nondemented LA group (0.8 ± 0.8 on the right, 0.6 ± 0.6 on the left; $p < 0.05$ by Mann-Whitney U test). The grading scores in the right external capsule and the right anterior periventricular area were higher in the BD group (2.5 ± 0.8 and 3.0 ± 0.2, respectively) than in the nondemented LA group (1.6 ± 1.2 and 2.6 ± 0.5, respectively; $p < 0.05$).

Discussion

In an earlier report on the hyperintense lesions in CADASIL, no difference was observed in their distribution from those in the nonhereditary patients [14]. In contrast, O'Sullivan et al. [9] pointed out the diagnostic significance of temporopolar and external capsular lesions in CADASIL. The diagnostic value of these lesions has also been shown in differentiating CADASIL from multiple sclerosis [15]. However, external capsular lesions are frequently found in subjects with nondemented LA and BD, and thus their diagnostic specificity is estimated to be only 45%. Furthermore, a recent statistical parametric mapping analysis indicated that the hyperintense lesions in the temporopolar and medial frontopolar areas were significantly increased in comparison to BD, but not in the external capsule [10].

Until recently, more than 10 unrelated families with CADASIL have been reported in the Japanese population [16–20]. However, no information is available with respect to CADASIL-specific lesions in these patients. The present study revealed high specificity and sensitivity for these temporopolar lesions in Japanese CADASIL patients. In the nondemented LA and BD groups, only 1 patient from each group was noted to have temporopolar lesions, and these 2 subjects did not have any similar family members in their pedigree or consanguinity of their parents even after scrutiny. In contrast, external capsular lesions were frequently observed not only in the CADASIL patients, but also in the nondemented LA and BD patients. Furthermore, medial frontopolar lesions were occasionally found in both CADASIL and BD patients. With respect to advancing age, the temporopolar lesions appeared at an early stage of the disease process and may be observed in patients in their 20s [21]. In accordance with this observation, the older sister of the proband of family 1 showed temporopolar lesions (indicated by arrows in fig. 2) without any medial frontopolar lesions.

The vulnerability of the temporopolar area in CADASIL patients is intriguing, but the reasons remain unclear in the present study. Ischemic LA is distributed mostly in the border zone between the medullary and lenticulostriate arteries, as well as in the terminal zone of the medullary arteries [7], and can be induced experimentally by chronic cerebral ischemia [22]. The subcortical white matter just beneath the temporal tip is doubly supplied by the subcortical arteries, and thus is expected to be resistant to chronic cerebral ischemia. In addition, the temporal lobe is the least-affected lobe in ischemic LA [23]. Therefore, temporopolar lesions may be causally related to the small vessel changes specific in CADASIL or alternatively to nonischemic causes. Auer et al. [10] reported that temporopolar lesions corresponded clinicopathologically to a widening of the perivascular space and gliosis. The specificity of temporopolar lesions in CADASIL patients is obvious, but further investigation is required to understand their pathogenetic mechanism.

There were no marked differences in the distribution of hyperintensities between the nondemented LA and BD groups. However, the lesions were less intense in the bilateral medial frontopolar regions, the right external capsule and the right anterior periventricular region in the nondemented LA group. The low prevalence of medial frontopolar lesions in the nondemented LA patients seems to be due to the relatively milder anterior periventricular lesions, because the medial frontopolar lesions extended from the anterior periventricular lesions.

In differentiating the various subtypes of small artery dementia, a diagnostic strategy for CADASIL patients is important. A *Notch 3* missense mutation is estimated to occur in 0.05% of the general Caucasian population [24] but is found in 90% of Caucasian CADASIL patients. In contrast, in Japan, a previous study indicated that the *Notch 3* mutation was found in only 25% of CADASIL-

like patients [11]. Sequencing the full-length *Notch 3* gene is not convenient considering that it is a giant gene consisting of 8 kbp, and various types of mutations may occur out of exons 3 and 4, which account for at most 70% of the CADASIL patients [8]. The electron-microscopic detection of granular osmiophilic material in the vascular wall is another method for diagnosis, but its sensitivity is not necessarily satisfactory. Temporopolar lesions, which have been shown to be specific for CADASIL in non-Caucasian patients, can serve as surrogate diagnostic markers before genetic analysis.

Acknowledgements

This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to H.T.). We are indebted to Miss Nakabayashi for her excellent technical assistance.

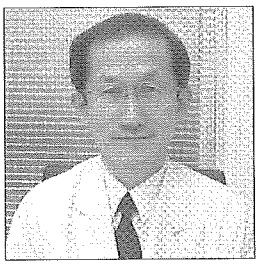
References

1 Jellinger K: The pathology of ischemic-vascular dementia: an update. J Neurol Sci 2002; 203:153–157.
2 Yanagihara T: Vascular dementia in Japan. Ann NY Acad Sci 2002;977:24–28.
3 Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M: Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45:1161–1168.
4 Knopman DS, Rocca WA, Cha RH, Edland SD, Kokmen E: Incidence of vascular dementia in Rochester, Minn, 1985–1989. Arch Neurol 2002;59:1605–1610.
5 Jellinger K, Neumayer E: Progressive subcorticale vasculare Encephalopathie Binswanger. Arch Psychiatr Nervenkr 1964;205:523–554.
6 Meyer JS, Kawamura J, Terayama Y: White matter lesions in the elderly. J Neurol Sci 1992; 110:1–7.
7 Pantoni L, Garcia JH: Pathogenesis of leukoaraiosis: a review. Stroke 1997;28:652–659.
8 Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF: Diagnostic strategies in CADASIL. Neurology 2002;59: 1134–1138.
9 O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS: MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology 2001;56: 628–634.
10 Auer DP, Putz B, Gossl C, Elbel G-K, Gasser T, Dichgans M: Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. Radiology 2001;218:443–451.
11 Santa Y, Uyama E, Chui DH, Arima M, Kotorii S, Takahashi K, Tabira T: Genetic, clinical and pathological studies of CADASIL in Japan: a partial contribution of *Notch3* mutations and implications of smooth muscle cell degeneration for the pathogenesis. J Neurol Sci 2003;212:79–84.
12 Fazekas F, Kleinert R, Offenbacher H, Payer F, Schmidt R, Kleinert G, Radner H, Lechner H: The morphologic correlate of incidental punctate white matter hyperintensities on MR images. AJNR Am J Neuroradiol 1991;12: 915–921.
13 Bennett DA, Wilson RS, Gilley DW, Fox JH: Clinical diagnosis of Binswanger's disease. J Neurol Neurosurg Psychiatry 1990;53:961–965.
14 Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, Tournier-Lasserve E, Bousser MG: Patterns of MRI lesions in CADASIL. Neurology 1998;51:452–457.
15 O'Riordan S, Nor AM, Hutchinson M: CADASIL imitating multiple sclerosis: the importance of MRI markers. Mult Scler 2002;8:430–432.
16 Kotorii S, Takahashi K, Kamimura K, Nishio T, Arima K, Yamada H, Uyama E, Uchino M, Suenaga A, Matsumoto M, Kuchel G, Rouleau GA, Tabira T: Mutations of the *Notch3* Gene in non-Caucasian patients with suspected CADASIL syndrome. Dement Geriatr Cogn Disord 2001;12:185–193.
17 Manabe Y, Murakami T, Iwatsuki K, Narai H, Warita H, Hayashi T, Shoji M, Imai Y, Abe K: Nocturnal blood pressure dip in CADASIL. J Neurol Sci 2001;193:13–16.
18 Nishio T, Arima K, Eto K, Ogawa M, Sunohara N: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: report of an autopsied Japanese case. Clin Neurol (Tokyo) 1997;37:910–916.
19 Takahashi K, Kotorii S, Chui DH, Shirotani K, Tabira T: *Notch3* gene in CADASIL syndrome: mutation frequencies in Japanese and its expression and processing; in Tanaka C, McGeer PL, Ihara Y (eds): Neuroscientific Basis of Dementia. Basel, Birkhäuser, 2001, pp 209–216.
20 Utatsu Y, Takashima H, Michizono K, Kanda N, Endou K, Mitsuyama Y, Fujimoto T, Nagai M, Umehara F, Higuchi I, Arimura K, Nakagawa M, Osame M: Autosomal dominant early onset dementia and leukoencephalopathy in a Japanese family: clinical, neuroimaging and genetic studies. J Neurol Sci 1997;147:55–62.
21 van den Boom R, Oberstein SL, Ferrari MD, Haan J, van Buchem MA: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR imaging findings at different ages – 3rd to 6th decades. Radiology 2003;229:683–690.
22 Tomimoto H, Ihara M, Wakita H, Ohtani R, Lin JX, Akiguchi I, Kinoshita M, Shibasaki H: Chronic cerebral hypoperfusion induces white matter lesions and loss of oligodendroglia with DNA fragmentation in the rat. Acta Neuropathol (Berl) 2003;106:527–534.
23 Akiguchi I, Tomimoto H, Wakita H, Kawamoto Y, Matsuo A, Ohnishi K, Watanabe T, Budka H: Topographical and cytopathological lesion analysis of the white matter in Binswanger's disease brain. Acta Neuropathol (Berl) 2004;107:563–570.
24 Dong Y, Hassan A, Zhang Z, Huber D, Dalagcorgou C, Markus HS: Yield of screening for CADASIL mutations in lacunar stroke and leukoaraiosis. Stroke 2003;34:203–206.

秋期特集―鑑別診断と治療の話題

■ 脳血管障害の鑑別と治療 ■

● 脳炎　● 慢性硬膜下血腫　● てんかん　● 脳腫瘍　● 脱髄性疾患　● 脳卒中発作を伴うミトコンドリア脳筋症(MELAS)　● Creutzfeldt-Jakob病　● 片頭痛　● Reversible posterior leukoencephalopathy syndrome(RPLS)　● 代謝性脳症　● Wernicke脳症　● 神経Behçet病　● サルコイドーシス



兵庫医科大学総合診療内科学　立花（たちばな）　久大（ひさお）(教授)－写真－，川端（かわばた）　啓太（けいた）

INTRODUCTION

脳血管障害は一般に急激に発症することが多く，意識障害や何らかの局所神経症状を呈する。一方，脳血管障害に特徴的な急性発症や局所神経症状を呈しても，原因が脳血管障害でない症例もときに経験する。脳血管障害と診断する際には，常に鑑別診断としてこのような疾患を念頭に置く必要がある。本稿ではこれら脳血管障害類似の症状を呈する疾患についてそれらの特徴と治療について述べる。

1 脳炎

脳炎でも局所性に炎症が強く集中し脳局所症状が前景に出る場合もある。その代表的なものとして単純ヘルペス脳炎がある。

単純ヘルペス脳炎の発症は急性で発熱，頭痛，けいれん発作などで始まり，次いで失語や片麻痺，精神症状(人格変化，行動異常，幻覚など)などを呈する。約2割の患者では脳症状で始まるため，脳血管障害との鑑別が必要となる。単純ヘルペス脳炎では側頭葉，前頭葉眼窩回，大脳辺縁系が障害されやすいため，CT，MRI，脳波におけるこれら好発部位の病変が診断上有力な所見となる(図1)。診断には血清，髄液の酵素抗体(ELISA)などの抗体を参考にするが，髄液からのPCRによるウイルスゲノムの検出が有用である。本症の致命率は10～30%で，重篤な後遺症を伴うことが多い。そのため本症を疑った場合迅速に抗ウイルス療法(アシクロビル)を開始する。脳浮腫，けいれんに対しても適切に対処する。

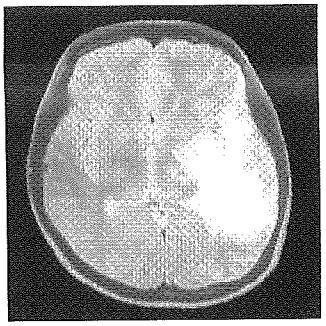


図1　単純ヘルペス脳炎(MRI T_2強調画像)
23歳女性。健忘と言語障害で発症。左側頭葉に高信号域を認める。

2 慢性硬膜下血腫

軽い外傷後3週以上の経過で，架橋静脈からの血液が硬膜下腔に貯留し症状を呈す。高齢者に多く，外傷の既往のはっきりしない場合も約30%に存在する[1]。片麻痺や失語症などの神経症状や，軽度の認知症などの精神症状が比較的急性に出現し，症状に日内変動が見られることも多い。突発的に巣症状や意識変容を来し，脳血管障害と誤診することもある。CT(特に造影)，MRIにて診断は容易である。ただ両側性血腫の場合，正中偏位がなく脳室が狭小化して脳溝がほとんど確認できない像で，年齢に比し極めて正常すぎる画像を呈することがあり，判読上注意が必要である。

治療としては血腫吸引手術を行う。症状出現が急性である場合や，脳圧亢進が高度である場合は緊急手術の適応となる。

3 てんかん

てんかんの中でも特に部分発作は，一側大脳半球の一部に限局したてんかん源に由来する発作で，局所性脳症状を呈するため，脳血管障害の初発症状と鑑別する必要がある。部分発作後，発作に巻き込まれた領域に数分から数時間限局性麻痺が残ることがあり，Todd麻痺(Todd's paralysis)として知られている。部分運動発作がずっと持続する持続性部分てんかんも脳血管障害と鑑別する必要がある。このタイプの発作に対してはカルバマゼピンまたはフェニトインが第一選択薬となる。抗てんかん薬の効果は発作型によりかなり異なるので，まず発作型を正確に診断することが大事である。

4 脳腫瘍

最も悪性度の高いグリオーマである多形膠芽腫(glioblastoma multiforme)は，腫瘍組織内に出血や血栓形成による壊死，軟化巣を生じることがあるため，通常の脳血管障害との鑑別が必要なことがある。初期には画像上も脳血管障害と区別しにくいことがある。大脳半球では特に側頭葉，次いで前頭葉に起りやすい。

第3脳室のコロイド嚢腫(colloid cyst)や頭蓋咽頭腫，松果体腫瘍はMonro孔や中脳水道を急に閉塞することにより突然，頭痛，けいれん，意識障害を来すことがある。通常画像上で容易に鑑別しうる。

まれではあるが脳腫瘍内出血により，脳血管障害発作のように突然意識障害で発症する場合がある。特に頻度が高く，また意識障害を来しうる腫瘍内出血は下垂体腺腫内出血(下垂体卒中)である。突然激烈な頭痛，眼球運動障害，急激な視力低下を来し，ときに大量出血やくも膜下出血を起すことがあり，ショック症状を示したり，意識障害を来す。

脳腫瘍の治療については，頭蓋内圧亢進症状や局所症状が強い場合や急速に進行している場合には緊急な対策が必要である。脳浮腫，けいれん発作の治療のほか脳室ドレナージ，腫瘍摘出などの手術療法を行う。

5 脱髄性疾患

多発性硬化症の発症は亜急性であることが多いが，大脳，脳幹症状が急性に発症することもあり，脳血管障害との鑑別が困難なこともある。診断には髄液のγグロブリン上昇，ミエリン塩基性タンパク質上昇，オリゴクローナールバンドの存在などを参考にする。

急性散在性脊髄炎(ADEM)は急性に発症する脳脊髄の炎症性疾患で，散在性に病変を生じる。発熱，意識障害を生じ，多彩な神経症状を示すことが多い。いずれの疾患とも急性期にはステロイドパルス療法を行い，その後，ステロイドの漸減療法を行う。

6 脳卒中発作を伴うミトコンドリア脳筋症(MELAS)

MELASはミトコンドリアDNA異常を原因とする疾患である。脳症，高乳酸血症，脳卒中様発作を中核とするため，特に若年者の脳血管障害鑑別上忘れてはならないものである[2,3]。脳卒中様症状としては，けいれん，意識障害，視野・視力障害，片麻痺などがある。また初発症状として，片頭痛様の発作性頭痛や嘔吐発作を認めることも多い。その他感音性難聴，多毛，低身長を呈することも多い。血液，髄液中の乳酸高値を認め，画像上，病巣が血管の支配領域に一致しないことや灰白質を中心に病変が広がる点が特徴である(図

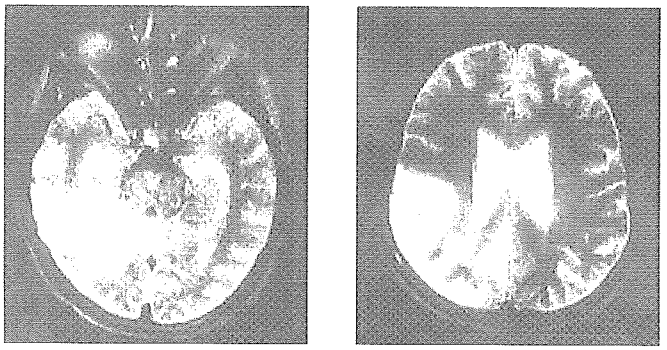


図2 ミトコンドリア脳筋症（MRI T_2強調画像）
25歳男性。左同名性半盲と軽度左片麻痺にて発症。右側頭葉～頭頂葉～後頭葉にかけ血管支配に一致しない高信号域を認める。

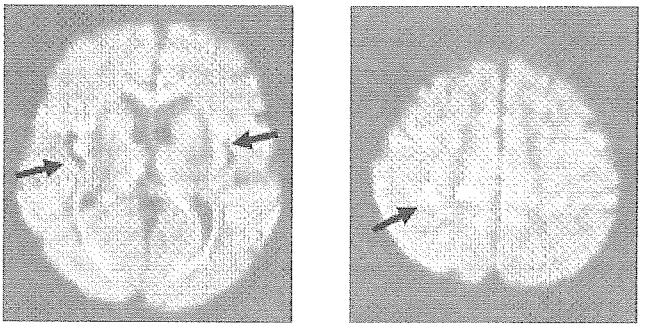


図3 Creutzfeldt-Jakob病（MRI 拡散強調画像）
67歳女性。2月言語障害出現。4月言語障害増悪と歩行障害出現したため入院。両側の島，右前頭葉内側皮質に高信号域を認める。

2）。脳卒中様発作については通常の脳梗塞の治療に準ずる。急性期に補液を行う際には乳酸を含むものは使用しない。

7 Creutzfeldt-Jakob病

プリオン病の1つであるCreutzfeldt-Jakob病は亜急性に進行する認知症を中核とし，多彩な神経症状を呈する。しかし，約10%の症例では脳血管障害と誤診されるほど急性の認知症症状や視覚異常（視覚障害，視野障害，変形視，色覚異常）が前景に出る場合がある。比較的早期においてもMRI拡散強調画像にて萎縮を伴わない大脳皮質，尾状核，被殻，視床の高信号化が見られる（図3）。その他，髄液検査での14-3-3タンパク質の検出，ニューロン特異的エノラーゼ（NSE）の定量などが診断に有用である。脳波上有名な周期性同期性放電（PSD）はかなり進行しないと見られない。現在のところ有効な治療法はなく対症的に治療するのみである。

8 片頭痛

前兆を伴う片頭痛では大脳皮質あるいは脳幹部の障害によると考えられる神経症状（前兆：視野障害，一側の知覚，運動障害，失調など）が5～20分にわたり徐々に進行し60分以内に治まり，頭痛や悪心などが出現する。前兆

表1　代謝性脳症を呈しうる疾患

Ⅰ．意識障害を呈する代謝性疾患
　A　低酸素性一低血圧性脳症
　B　高炭酸ガス血症
　C　低血糖
　D　高血糖
　E　肝不全
　F　Reye症候群
　G　尿毒症
　H　糖尿病あるいは腎不全によるアシドーシス
　I　Addison病
　J　ビスマス中毒
Ⅱ．ナトリウム・カリウム異常症：浸透圧変化
Ⅲ．進行性錐体外路症候群を呈する代謝性疾患
　A　後天性肝脳変性症
　B　高ビリルビン血症，核黄疸
　C　副甲状腺機能低下症
Ⅳ．小脳失調症を呈する代謝性疾患
　A　甲状腺機能低下症
　B　高体温症，低体温症
　C　Celiac病
Ⅴ．精神症状や痴呆を呈する代謝性疾患
　A　Cushing病，ステロイド脳症
　B　甲状腺性精神病
　C　副甲状腺機能亢進症
　D　膵性脳症(？)
　E　Whipple病

を伴う片頭痛では，片麻痺を呈する片麻痺型片頭痛や眼球運動障害による複視を認める眼筋麻痺性片頭痛，脳幹部障害に起因する前兆を認める脳底型片頭痛などがある。前兆のみで頭痛を伴わないものや突発性前兆を伴う片頭痛もあり，通常の一過性脳虚血発作を除外する必要がある。

前兆の時期にトリプタン製剤を服用しても頭痛出現時の時間と有効性にかわりがないことから，前兆の時期に服用せず頭痛が出現してから服用させる。片麻痺性片頭痛，脳底型片頭痛，遷延性前兆を伴う片頭痛，片頭痛性梗塞など重篤な神経症状を来す危険のある特殊な片頭痛の場合，予防療法の適応となる。

9 Reversible posterior leukoencephalopathy syndrome(RPLS)

高血圧性脳症や子癇により，頭痛，意識障害，けいれん，視力障害などを呈する症候群である[3]。同様の症状は免疫抑制剤の使用や腎障害によっても起こる。脳血管障害との鑑別が困難な例も少なくない。

RPLSの本態は血管性浮腫である。CT，MRIなどの画像検査では後頭葉白質を中心に梗塞巣を伴わない浮腫が一過性に出現する。

治療は迅速な降圧，抗脳浮腫療法や原疾患の治療，抗けいれん薬投与などの対症療法が中心となる。RPLSは基本的に可逆性病変なので，適切かつ迅速な治療が行われれば後遺症は残さない。

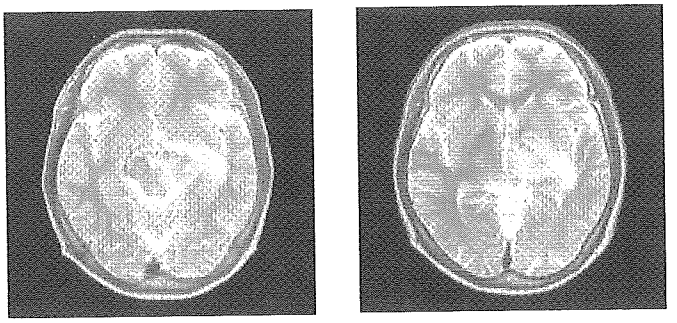


図4　神経Behçet病(MRI T_2強調画像)
55歳男性。Behçet病にて加療中，数秒間の意識消失発作(目をむいて呼びかけにも反応せず)のため来院。左大脳脚～内包～基底核にかけ高信号域が認められる。

10 代謝性脳症

種々の程度の意識障害を呈するため脳血管障害との鑑別が必要な場合がある。本症においては一般に左右差がないことが重要であるが，高血糖，低血糖などでは不随意運動や麻痺などが一過性に見られることがあるので留意する必要がある。本症でよく見られる不随意運動としては固定姿勢保持困難(asterixis)，ミオクローヌス，四肢振戦であるが，ときに片側性に見られることもある。橋本病で脳血管障害様の症状増悪を認めた例も報告されている。代謝性脳症を呈する原因疾患を表1に示す[3]。本症の診断の基本は器質性脳疾患を除外することと原因疾患を見つけだすことである。

11 Wernicke脳症

Wernicke脳症はビタミンB_1(サイアミン)の欠乏によって発症し，急性の意識障害，眼球運動障害，失調性歩行などを呈する。本症はかつては慢性アルコール中毒患者に限定されていたが，ビタミンを含まない中心静脈栄養や様々な手術後の合併症として発症することが見いだされるようになってきている。診断上有用なのは血中トランスケトラーゼ活性の低下，および活性型サイアミン添加で血中トランスケトラーゼ活性が上昇するというサイアミンピロリン酸効果測定である。MRIでは第3脳室周囲の視床，中脳水道周囲にT_2強調画像やプロトン強調画像で高信号を呈する病巣として描出される。治療としては一刻も早いビタミンB_1大量療法が望まれる。遅れると記憶障害，作話などのコルサコフ症候群が認められる。

12 神経Behçet病

神経Behçet病の中には中枢性運動麻痺，脳幹・小脳症状で発症するものがあり，精神症状や，動眼神経，滑車神経，外転神経の麻痺による外眼筋麻痺や，顔面神経麻痺なども見られる。MRI上，急性期には大脳基底核，深部白質，大脳脚，橋底部などにT_2強調画像で高信号を呈する病巣として描出される(図4)が，これらは炎症(血管炎)や浮腫による変化と考えられている。

治療は中等～大量の副腎皮質ステロイド投与を行う。治療抵抗性のものは約30%あり，脳卒中様発作をくりかえし認知症へと進行することがある。Behçet病には大動脈～脳主幹動脈に動脈炎や動脈瘤を生じこれを引き金として脳梗塞を発症する場合や，血液凝固能の亢進により脳静脈洞血栓症をおこす血管Behçet病といわれるタイプもある。このような場合，ステロイド，免疫抑制剤のほか，抗血小板剤や抗凝固剤の併用療法が必要となる。

13 サルコイドーシス

サルコイドーシスの中枢性病変は髄膜脳炎型が多く，脳底部に病変が強く，視床下部や下垂体，脳幹の機能障害を来す。脳幹部では脳神経根部(特にⅦ，Ⅷ)に病変が顕著に現れる。また，脳実質にサルコイド結節が散在するびまん性転移性病巣性脳炎型の場合は，けいれん発作，精神症状，記銘力障害，失語・失行・失認などの多彩な神経症状が出現する。神経合併症が生じたら，ステロイドを導入することが原則である。

文　献

1) 廣瀬源二郎：脳血管障害の臨床．脳血管障害と鑑別が必要な疾患．日医師会誌特別号 125：S90-S94，2001
2) 立花久大：若年者脳梗塞の診断と治療．脳梗塞後遺症の新しい診断・治療指針．急性期・慢性期(亀山正邦編)，p125-138．医薬ジャーナル社，大阪，2001
3) 立花久大：脳血管障害の症候と診断．鑑別診断．新しい診断と治療のABC 10，脳血管障害(神経1(福内靖男編))，p67-76．最新医学社，東京，2003
4) Hinchey J, et al：A reversible posterior leukoencephalopathy syndrome, N Engl J Med 334：494-500, 1996