

## Differences in regional cerebral blood flow in two types of leuko-araiosis

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### Abstract

Cerebral blood flow and cerebrovascular acetazolamide reactivity were investigated in patients with periventricular hyperintensity and in patients with leuko-araiosis in centrum semiovale. Fifteen patients with periventricular hyperintensity, 15 patients with leuko-araiosis in centrum semiovale and 15 age-matched controls without leuko-araiosis were studied. The regional cerebral blood flow was measured using the stable xenon CT method before and 20 min after intravenous injection of 17mg/kg acetazolamide. The blood flow and the cerebrovascular acetazolamide reactivity in the area of leuko-araiosis were significantly lower in the periventricular hyperintensity group and the leuko-araiosis in centrum semiovale group than the control group. The blood flow in the cerebral cortex was significantly lower in the leuko-araiosis in centrum semiovale group than in the periventricular hyperintensity group and the control group. The cerebrovascular acetazolamide reactivity in the cerebral cortex did not show any significant difference among the three groups. The blood flow in the cerebral cortex was decreased in patients with leuko-araiosis in centrum semiovale but the cerebrovascular acetazolamide reactivity in the cerebral cortex was normal in patients with leuko-araiosis. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* Leuko-araiosis; Periventricular hyperintensity; Cerebral blood flow; Acetazolamide

### 1. Introduction

Leuko-araiosis [1] is a radiological finding and its pathophysiology is not uniform [2]. Leuko-araiosis may be divided into two types; periventricular hyperintensity and leuko-araiosis in centrum semiovale [2–5]. The disturbance in cerebrospinal fluid circulation may be related to periventricular hyperintensity and hypertension may be related to leuko-araiosis in centrum semiovale [6]. The two types may have some difference in cerebral circulation. In order to find out the difference, we investigated cerebral blood flows and cerebrovascular acetazolamide reactivity in the two types of leuko-araiosis.

### 2. Patients and methods

Fifteen cases of periventricular hyperintensity (A), 15 cases of leuko-araiosis in centrum semiovale (B) and 15

age-matched controls without leuko-araiosis (C) were studied with their informed consent. The patients with leuko-araiosis were admitted to our hospital and head computed tomography (CT), head magnetic resonance imaging (MRI), echocardiography and blood viscosity were studied on the patients. A is defined as hyperintensity areas in head MRI which are contiguous to the ventricles (Fig. 1) and B is defined as hyperintensity areas in head MRI which are located at a distance from the ventricles (Fig. 2). The patients who have both A and B, the patients who have signs or symptoms of cerebral infarction, and the patients with hydrocephalus and leukodystrophy were excluded from this study. Medications which influence cerebral blood flow were discontinued 2 weeks prior to the cerebral blood flow examination. Fifteen cases in each group were selected by the order of admission date. Table 1 shows the subjects' characteristics in the three groups. The total volume of leuko-araiosis on MRI was determined according to the method of Waldemar et al. [7].

The regional cerebral blood flow was measured using the stable xenon CT method [8–11]. The basal ganglia

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Fig. 1. Axial and coronal sections of  $T_2$ -weighted image and proton density image of head MRI in a patient with periventricular hyperintensity (A). Hyperintensity areas are contiguous to the ventricles.

section and the lateral ventricle section parallel to the orbito-meatal line were studied. The subjects inhaled room air followed by a mixture of 30% xenon and 50% oxygen for 3 min. Serial scanning was performed once before xenon inhalation, three times in the wash-in process and five times in the washout process of 5 min. The serial scanning program consisted of a total of 18 scans consisting of nine serial scans on each section. The xenon concentration in the end-tidal expired gas was continuously recorded by the thermoconductivity method. We used the xenon delivery and analysis system (AZ-7000 model, Anzai Sogyo, Tokyo, Japan) and the CT equipment (PreSage, Yokogawa Medical Systems, Tokyo, Japan). Regional cerebral blood flows were measured in the leuko-araiosis area, and in the cerebral cortex and cerebral white matter where the influence of the leuko-araiosis was considered to be little. Round region of interest (ROI) with a diameter of 7 mm was used and the ROI was placed in the center of each leuko-araiosis area in bilateral anterior and posterior regions. The leuko-araiosis area blood flow was calculated as the average of the blood flows in the four leuko-araiosis areas. In bilateral frontal lobes, parietal lobes, temporal lobes and occipital lobes, the ROI was placed in the area where leuko-araiosis was not adjacent.

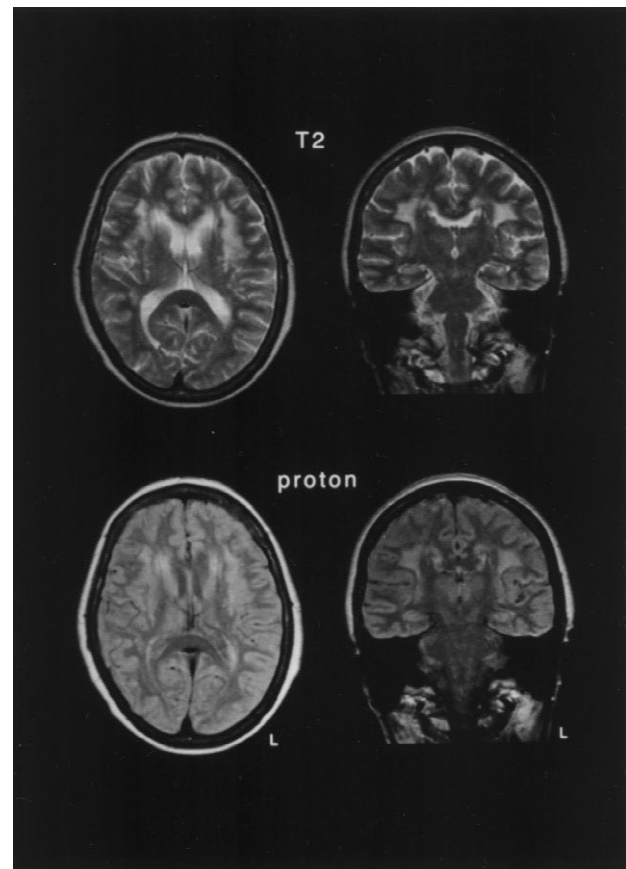


Fig. 2. Axial and coronal sections of  $T_2$ -weighted image and proton density image of head MRI in a patient with leuko-araiosis in centrum semiovale (B). Hyperintensity areas are located at a distance from the ventricles.

The cerebral cortex blood flow and cerebral white matter blood flow were calculated as the average of the blood flows in the eight areas.

The regional cerebral blood flow was measured before and 20 min after intravenous injection of 17mg/kg acetazolamide. Mini-mental state examination [12] was performed and underlying diseases were examined.

Statistical analysis was performed using Mann-Whitney's  $U$ -tests for comparison of the cerebral blood flows and using Fisher's exact probability tests for comparison of underlying diseases among the three groups.

### 3. Results

Fig. 3 shows the actual records of xenon CT in A, B, and C before and after injection of acetazolamide. Before injection of acetazolamide, the blood flow in the leuko-araiosis area is lower than that in the cerebral white matter. The blood flow in the cerebral cortex is lower in B than in A and C. After injection of acetazolamide, the blood flow is increased. The increase rate in blood flows by acetazola-

Table 1  
Subjects' characteristics in three groups

	(A) Periventricular hyperintensity group	(B) Leuko-araiosis in centrum semiovale group	(C) Age-matched control group
Number of subjects	15	15	15
Age (years) <sup>a</sup>	66.8±8.4	63.2±8.3	65.1±8.5
Male:female	8:7	7:8	7:8
Hypertension	6/15	12/15*	4/15
Diabetes mellitus	7/15	8/15	3/15
Hyperlipidemia	5/15	6/15	3/15
Mini-mental state examination score <sup>a</sup>	26±3	18±4	30±0
Total volume of leuko-araiosis on MRI (cm <sup>3</sup> ) <sup>a</sup>	7.1±4.3	6.5±4.2	–

<sup>a</sup> Mean±standard deviation.

\*  $P<0.05$  versus B,  $P<0.01$  versus C.

side is lower in the leuko-araiosis area than in the cerebral white matter.

Table 2 shows the mean and standard deviation of the blood flows in the cerebral cortex, cerebral white matter and leuko-araiosis area. The blood flow in the leuko-araiosis area was significantly lower than that in the cerebral white matter. The blood flow in the cerebral cortex was significantly lower in B than in A and C. The increase rate in blood flows by acetazolamide was significantly lower in the leuko-araiosis area than in the cerebral white matter.

The rate of association of hypertension was significantly higher in B than in A and C (Table 1). There was no significant correlation between hypertension and cerebral blood flow in the three groups. There was no significant difference in total volume of leuko-araiosis on MRI (Table 1).

#### 4. Discussion

Leuko-araiosis has many causes [2] but the common causes are considered to be arteriolosclerosis [13–15] and normal aging [16–18]. Cerebral blood flow has been reported to be decreased in leuko-araiosis [19–22].

Leuko-araiosis may be divided into two types; A and B [2–5]. The mechanism of the two types is considered to be different [4,5]. There was no report on the difference in cerebral blood flow between the two types. The blood flow in the cerebral cortex was significantly lower in B than in A and C. Because the total volume of leuko-araiosis on MRI did not show any significant difference between the two groups, the difference in blood flow in the cerebral cortex between the two groups is considered to be not due to the amount of leuko-araiosis but due to the location of leuko-araiosis.

Xenon CT with the wash-in/washout protocol has been reported to show considerable reliability in measuring blood flow in the cerebral white matter [9] and has been used in patients with pathological conditions [10,23,24]. Using the same instrument and the same method of xenon CT as ours, Haku et al. [25] reported a significant correlation ( $r=0.68$ ,  $P<0.001$ ) between regional cerebral blood flow values (10–30 ml/100 g/min) of the white matter area obtained by xenon CT and those of <sup>133</sup>Xe single-photon emission CT, which has been accepted as a standard method for the measurement of regional cerebral blood flow.

Acetazolamide is considered to dilate the cerebral arterioles by inhibiting the carbonic anhydrase in the red

Table 2

Blood flow (ml/100g/min) before the intravenous injection of acetazolamide and increase rate (%) in blood flow by the intravenous injection of acetazolamide (mean±standard deviation)

	(A) Periventricular hyperintensity group	(B) Leuko-araiosis in centrum semiovale group	(C) Age-matched control group
<i>Before the intravenous injection of acetazolamide</i>			
Cerebral cortex blood flow	50.1±7.2	41.9±7.1*	57.9±7.5
Cerebral white matter blood flow	25.6±4.3	25.2±4.2	28.4±4.4
Leuko-araiosis area blood flow	16.9±2.8**	17.1±2.9**	–
<i>After the intravenous injection of acetazolamide</i>			
Increase rate in cerebral cortex blood flow	52.1±7.5	58.2±8.2	56.2±8.0
Increase rate in cerebral white matter blood flow	45.9±6.8	45.9±7.2	47.1±7.5
Increase rate in leuko-araiosis area blood flow	31.6±7.4**	29.7±6.8**	–

\*  $P<0.01$  compared with the other two groups.

\*\*  $P<0.01$  compared with the cerebral white matter.

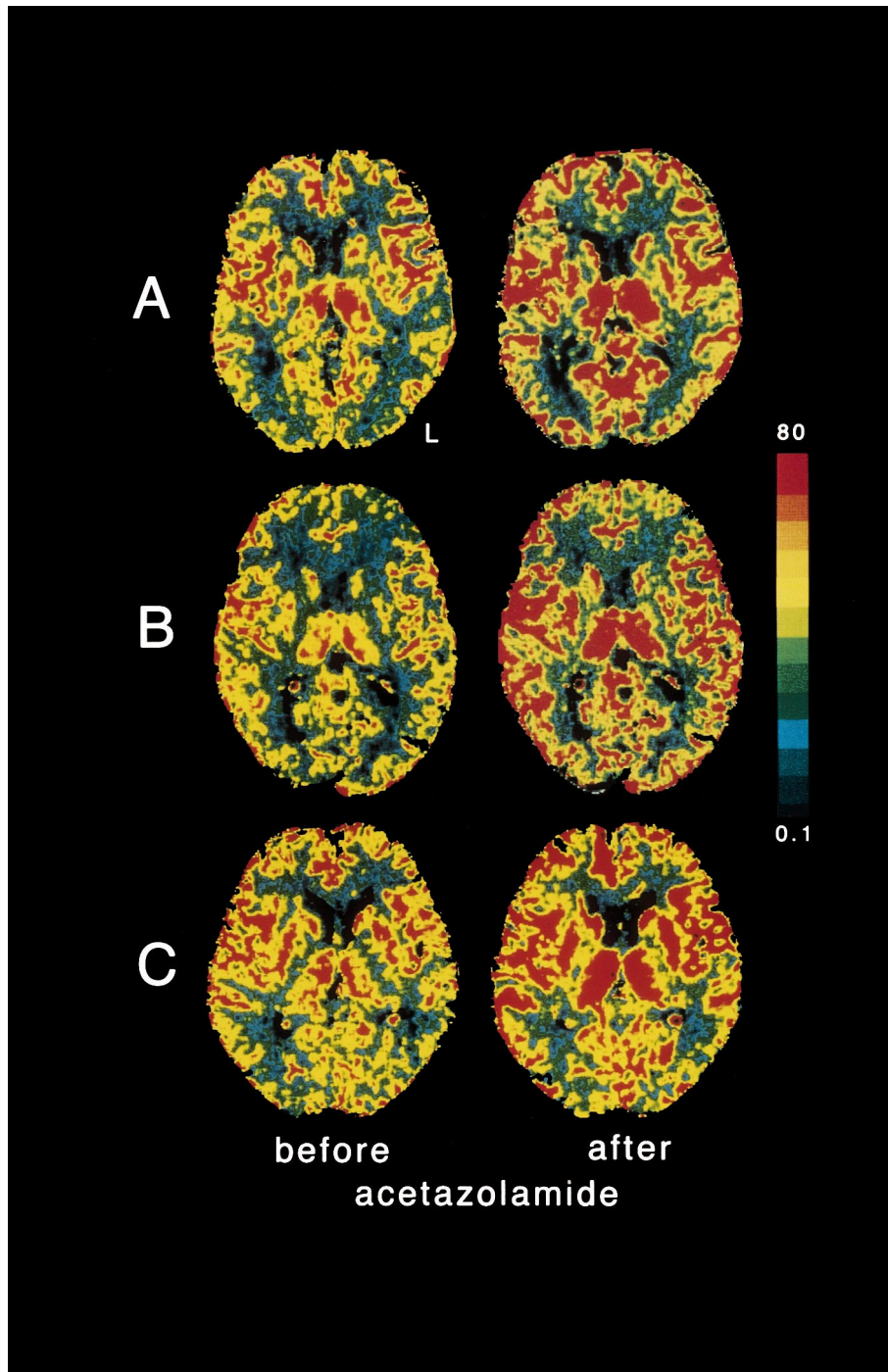


Fig. 3. Actual records of xenon computed tomography before and after intravenous injection of acetazolamide. (A) Periventricular hyperintensity, (B) leuko-araiosis in centrum semiovale, (C) age-matched control without leuko-araiosis.

blood cells and increasing  $\text{CO}_2$  in the arterioles [26,27]. Acetazolamide has been used for examining cerebrovascular dilatory reserve capacity [28].

In the present study, cerebrovascular acetazolamide reactivity was decreased in the leuko-araiosis area. This suggests that cerebrovascular dilatory reserve capacity is decreased in the leuko-araiosis area. The cerebrovascular acetazolamide reactivity in the cerebral cortex did not

show any significant difference among the three groups. This suggests that cerebrovascular dilatory reserve capacity is preserved in the cerebral cortex and that decreased cerebral cortex blood flow may be due to overlying cortex diaschisis in cases of B.

The present study showed that the blood flow in the cerebral cortex was lower and the rate of hypertension was higher in B than in A. This suggests that hypertension and

arteriolosclerosis are related more to B than A and that the pathogenesis of the two types is different. Because the sample size is small in the present study, we hope that a study in a large sample size will be performed.

## References

- [1] Hachinski VC, Potter P, Merskey H. Leuko-araiosis: An ancient term for a new problem. *Can J Neurol Sci* 1986;13:533–4.
- [2] Verny M, Duyckaerts C, Pierot L, Hauw J-J. Leuko-araiosis. *Dev Neurosci* 1991;13:245–50.
- [3] Bowen BC, Barker WW, Loewenstein DA, Sheldon J, Duara R. MR signal abnormalities in memory disorder and dementia. *Am J Radiol* 1990;154:1285–92.
- [4] Miyao S. Leuko-araiosis: concept and its clinical relevance (in Japanese). *Nihon Rinsho* 1993;51:551–7.
- [5] Ohsawa N, Takahashi S, Yonezawa H. Cerebral blood flow patterns in patients with leukoaraiosis and lacunar infarction (in Japanese). *Rinsho Shinkei* 1994;34:443–8.
- [6] Oishi M, Mochizuki Y, Takasu T. Difference in P300 latency in two types of leukoaraiosis. *J Neurol* 1997;244:646–50.
- [7] Waldemar G, Christiansen P, Larsson HBW, Høgh P, Laursen H, Lassen NA, Paulson OB. White matter magnetic resonance hyperintensities in dementia of the Alzheimer type: morphological and regional cerebral blood flow correlates. *J Neurol Neurosurg Psychiatry* 1994;57:1458–65.
- [8] Johnson DW, Stringer WA, Marks MP, Yonas H, Good WF, Gur D. Stable xenon CT cerebral blood flow imaging: rationale for and role in clinical decision making. *Am J Neuroradiol* 1991;12:201–13.
- [9] Kashiwaki S, Yamashita T, Nakano S, Kalender W, Polacin A, Takasago T, Eguchi Y, Ito H. The wash-in/washout protocol in stable xenon CT cerebral blood flow studies. *Am J Neuroradiol* 1992;13:49–53.
- [10] Oishi M, Mochizuki Y, Hara M, Du C-M, Takasu T. Effects of intravenous L-dopa on P300 and regional cerebral blood flow in parkinsonism. *Int J Neurosci* 1996;85:147–54.
- [11] Oishi M, Mochizuki Y, Hara M, Takasu T. Central motor conduction time in patients with periventricular lucencies. *J Neurol Sci* 1996;142:30–5.
- [12] Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state' a practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 1975;12:189–98.
- [13] Hijdra A, Verbeeten Jr. B, Verhulst JAMP. Relation of leukoaraiosis to lesion type in stroke patients. *Stroke* 1990;21:890–4.
- [14] Yao H, Sadoshima S, Ibayashi S, Kuwabara Y, Ichiya Y, Fujishima M. Leukoaraiosis and dementia in hypertensive patients. *Stroke* 1992;23:1673–7.
- [15] van Swieten JC, van den Hout JHW, van Ketel BA, Hijdra A, Wokke JHJ, van Gijn B. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. *Brain* 1991;114:761–74.
- [16] Kawamura J, Meyer JS, Terayama Y, Wethers S. Leuko-araiosis correlates with cerebral hypoperfusion in vascular dementia. *Stroke* 1991;22:609–14.
- [17] Chimowitz MI, Awad IA, Furlan AJ. Periventricular lesions on MRI: facts and theories. *Stroke* 1989;20:963–7.
- [18] Hunt AL, Orrison WW, Yeo RA, Haaland KY, Rhyne RL, Garry PJ, Rosenberg GA. Clinical significance of MRI white matter lesions in the elderly. *Neurology* 1989;39:1470–4.
- [19] Kobayashi S, Okada K, Yamashita K. Incidence of silent lacunar lesion in normal adults and its relation to cerebral blood flow and risk factors. *Stroke* 1991;22:1379–83.
- [20] National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990;21:637–76.
- [21] Kobari M, Meyer JS, Ichijo M, Oravez WT. Leukoaraiosis: Correlation of MR and CT findings with blood flow, atrophy, and cognition. *Am J Neuroradiol* 1990;11:273–81.
- [22] de Reuck J, Decoo D, Lemahieu I, Strijckmans K, Goethals P. Is the leuko-araiosis-dementia syndrome different from Binswanger's subcortical atherosclerotic encephalopathy? *J Stroke Cerebrovasc Dis* 1992;2:225–7.
- [23] Kawamura J, Terayama Y, Takashima S, Obara K, Pavol MA, Meyer JS, Mortel KF, Weathers S. Leuko-araiosis and cerebral perfusion in normal aging. *Exp Aging Res* 1993;19:225–40.
- [24] Mochizuki Y, Oishi M, Hara M, Yoshihashi H, Takasu T. Regional cerebral blood flow in lacunar infarction. *J Stroke Cerebrovasc Dis* 1997;6:137–40.
- [25] Haku T, Hosoya T, Komatani A, Watanabe N, Yamaguchi K. Correlation of regional cerebral blood flow between Xe-CT and <sup>133</sup>Xe-SPECT: validity of Xe-CT in evaluating rCBF [in Japanese with English abstract]. *Nippon Acta Radiol* 1996;56:828–33.
- [26] Vorstrup S, Henriksen L, Paulson OB. Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate for oxygen. *J Clin Invest* 1984;74:1634–9.
- [27] Frankel HM, Gracia E, Malik F, Weiss JK, Weis HR. Effect of acetazolamide on cerebral blood flow and capillary patency. *J Appl Physiol* 1992;73:1756–61.
- [28] Sullivan HG, Kingsbury TB, Morgan ME, Jeffcoat RD, Allison JD, Goode JJ, McDonnell DE. The rCBF response to Diamox in normal subjects and cerebrovascular disease patients. *J Neurosurg* 1987;67:525–34.