Correlations of leuko-araiois with cerebral atrophy and perfusion in elderly normal subjects and demented patients

Jun Kawamura, John S Meyer, Makoto Ichijo, Masahiro Kобari, Yasuo Terayama, Susan Weathers

Abstract

CT images of leuko-araiois in brain slices were quantified according to volumes of reduced Hounsfield units in frontal peri-ventricular white matter in groups of elderly patients with multi-infarct dementia (MID, n = 23) and dementia of the Alzheimer type (DAT, n = 16). Volumes of leuko-araiois, estimates of atrophic cerebral tissue, and local cerebral perfusion utilising inhalation of xenon gas as the indicator were correlated on the same CT slices. Ratios of frontal leuko-araiois to total brain tissue volume were similar for patients with MID and DAT (mean 5.7 (SD 2.1)\% v 6.5 (3.2)\%), and both were significantly greater than ratios in elderly normal volunteers (3.1 (1.3)\%, 0 < 0.001). Cerebral atrophy (measured as the ratio of volumes of cerebrospinal fluid to total brain area) for DAT patients was 17.0 (6.7)\%, which was greater than for MID patients (12.5 (5.4)\%; p < 0.05) and both types of patients showed more cerebral atrophy than did age matched, elderly normal subjects. Cerebral perfusion was decreased in all regions measured in patients with MID and DAT compared with elderly normal subjects. Multivariate regression analyses correlated frontal leuko-araiois with reductions of local cerebral blood flow in subcortical grey matter (p < 0.025) in patients with vascular dementia but not in those with DAT. These quantitative measures implicate decreased perfusion due to atherosclerosis in territories supplied by the deep penetrating cerebral arteries in the pathogenesis of leuko-araiois in patients with vascular dementia, but suggest a different pathogenesis for leuko-araiois in Alzheimer's disease.

(J Neurol Neurosurg Psychiatry 1993;56:182-187)

Interest has been focused on periventricular lucencies of white matter of unknown origin detected by CT scanning of the brain since Hachinski termed them "leuko-araiois" in 1987 to emphasise their uncertain aetiology, but these white matter lesions were described as early as 1980.\(^3\) Leuko-araiois has been associated with ageing, hypertension, risk factors for stroke, a history of symptomatic cerebral ischaemia, minor neurological signs, and impaired cognitive performance.\(^4\) Since the advent of magnetic resonance imaging, white matter lesions have been detected even more frequently among neurologically normal and asymptomatic elderly subjects, confirming that white matter lesions are often clinically silent.\(^9\)\(^10\)

The pathogenesis of leuko-araiois and its relation to cerebral ageing and cognitive impairment remains unclear. Clinical and neuropathological observations have suggested that ischaemia of white matter may have an important role in the pathogenesis of leuko-araiois. Without methods to quantitate leuko-araiois, however, its severity could not be correlated with brain atrophy and local cerebral blood flow, although some indirect comparisons have been made.\(^1\)\(^2\)\(^12\)

The present study was designed to elucidate the pathogenesis of leuko-araiois by quantifying it and comparing it with brain atrophy and local cerebral blood flow (LCBF) among elderly demented patients and age-matched normal volunteers. Stable xenon contrast computed tomography of cerebral blood flow was used to measure local cerebral perfusion, and results were correlated with quantitative measurements of frontal leuko-araiois and the degree of cerebral atrophy determined on the same CT slices of the brain.

Subjects and methods

SUBJECTS

As summarised in table 1, 23 elderly patients with multi-infarct (MID) and 17 patients with dementia of Alzheimer type (DAT) were admitted to the study, and results were compared with 16 age-matched volunteers who were neurologically and cognitively normal. All subjects signed informed consent according to protocols approved annually by the Institutional Review Board of the Department of Veterans Affairs Medical Centre, Houston, Texas.

Participating subjects underwent similar assessments, which included medical and neurological examinations, cognitive capacity screening examinations (CCSE),\(^13\)\(^14\) Hachinski ischaemic index scoring,\(^13\)\(^15\) and clinical and laboratory testing to determine if any risk factors for stroke were present. Diagnosis of dementia was made according to recommendations of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R).\(^16\) Demented patients had to score consistently less than 24 on serial CCSE examinations. CCSE scores below 25 correlate well with impairments of activities of daily living and other neuropsychological and neurobehavioural test instruments,
including the Wechsler adult intelligence scale; they provide reliable quantitative indices for dementia. Diagnosis of MID required Hachinski ischaemic scores above 7. Confirmation of cerebral infarctions by CT and MRI was obtained only after clinical examination had been established in patients with MID.

Diagnosis of probable DAT met the criteria provided by the group work of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). To be classified as DAT, patients were required to have Hachinski ischaemic scores below 4 as well as an absence of cerebral infarctions confirmed by CT scanning.

Normal volunteers were recruited through articles in local magazines describing ongoing prospective studies of ageing and from lectures to community groups concerned with the problems of ageing. Criteria for normal volunteers included normal neurological and CSSE examinations; absence of history of stroke or neurological or psychiatric disorders; and exclusion by CT and MRI of intracranial abnormalities other than age-related cerebral atrophy. To obtain suitable age matching among subjects, normal volunteers below 55 years of age were excluded.

**MEASUREMENTS OF CEREBRAL BLOOD FLOW**

**Theoretical background**

Xenon gas is a lipid soluble x-ray contrast indicator which absorbs transmitted x-rays, so that its concentration in different tissues may be detected and quantified by CT scanning. After xenon has been inhaled, time dependent changes of its concentration in different brain tissues cause directly proportional changes in CT or Hounsfield numbers. Local changes in tissue concentrations of xenon gas over time are used to measure local cerebral blood flow according to the basic monoexponential equation described by Kety. According to Kety's model, time dependent increases of diffusible indicator of the brain may be represented by the formula:

\[
Ci(T) = \frac{iiki}{\sqrt{T}} \int_{0}^{T} Ca(t) e^{-k_{i}T - \alpha t} dt
\]

where \(Ca(t)\) is the arterial xenon concentration at time \(t\); \(Ca(max)\) the arterial xenon concentration at infinity; and \(\alpha\) the rate constant for arterial washout with xenon. LCBF is then calculated by

\[
LCBF = \frac{iiki}{\sqrt{T}} \int_{0}^{T} Ca(t) e^{-k_{i}T - \alpha t} dt
\]

**Procedure**

Local cerebral blood flow was measured in all subjects by serial CT scanning during inhalation of 27% stable xenon as the contrast agent for eight minutes (Xe CT-CBF method). The method has been reported previously. Patients and volunteers fasted for six hours before CBF measurements. Subjects reclined on the CT table while inhaling 100% oxygen for two to four minutes. In all subjects, CT levels for CBF measurements were selected to include frontal, temporal, and occipital cortex; caudate nucleus; putamen; and thalamus. In 8 of 16 elderly normal volunteers, 5 of 23 patients with MID, and 7 of 17 patients of DAT, LCBF values at a second level 10 mm above the basal ganglia were also measured concurrently. The second level included parietal cortex and parietal white matter. After two baseline non-contrasted CT scans for each CT level were obtained, seven CT scans for each CT level were recorded at one minute intervals between the second and eighth minutes of xenon gas inhalation utilising one of two high resolution rapid CT scanners (Somatom DR version H, Siemens Medical Systems, Iselin New Jersey, USA or Picker Synerview SX 1200, Picker International, Ohio, USA) and xenon gas delivery system (Enhancer 3000, Diversified Diagnostic Products, Houston, Texas). The CT scanning parameters were 96 kVp, 540 mAs, 8 mm slice thickness with five second scanning times for Somatom DR-H and 130 kVp, 140 mAs, 10 mm, two seconds for Picker Synerview for each scan in the serial CT measurements. End tidal partial pressures for xenon gas (PEXe) and carbon dioxide (PECO) were obtained from their respective percentage volume values and corrected for barometric pressure measured at the time of the LCBF measurements.

LCBF values were generated as colour coded images for each brain slice by using a desk top computer (Elegance 425i, Northgate Computer Systems, Minneapolis, MN, USA) programmed to utilise two control scans as baseline and seven postenhancement scans to determine local Xe tissue saturation curves by Kety's formula. The original CT images (512 x 512 pixels) were compressed to 128 x 128 voxels before LCBF values were calculated. Effective voxel areas covered for each brain slice are 1.82 x 1.82 mm for Siemens Somatom DR-H and 1.88 x 1.88 mm for Picker Synerview, hence the volumes of each voxel analysed were 26.5 mm³ and 35.5 mm³ according to the thickness of the CT slices used. By identifying specific anatomical locations on the plain CT images and by using the cursor, LCBF values representing 11 regions for each hemisphere (a total of 22 regions including frontal, temporal, parietal, and occipital cortex; caudate nucleus; putamen, and thalamus;

<table>
<thead>
<tr>
<th>Normal volunteers</th>
<th>Patients with MID</th>
<th>Patients with DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 16)</td>
<td>(n = 23)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td>Age (SD) age</td>
<td>67.2 (10.5)</td>
<td>64.4 (10.2)</td>
</tr>
<tr>
<td>Age range</td>
<td>54-86</td>
<td>51-80</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>5/11</td>
<td>14/9</td>
</tr>
<tr>
<td>Mean (SD) CCSE</td>
<td>29-0 (1-7)</td>
<td>20-8 (6-7)</td>
</tr>
</tbody>
</table>

MID = Multi-infarct dementia; DAT = Dementia of Alzheimer type.
frontal, parietal, and occipital white matter; and internal capsular white matter) were computed. Values for LCBF in cortical grey matter (average of frontal, temporal, and occipital cortex), subcortical grey matter (average of caudate, putamen, and thalamus), and white matter (average of frontal, occipital, and capsular white matter) at the level of the basal ganglia were also calculated. EEG and EKG were monitored throughout the CBF measurements.

QUANTIFICATION OF LEUKO-ARAIOSIS AND CEREBRAL ATROPHY

Hounsfield unit numbers for each CT voxel were obtained from the baseline pre-enhanced CT images at the level of the basal ganglia. With these values, volumes for leuko-araiosis in white matter adjacent to the anterior horns of both lateral ventricles and anterior to the heads of both caudate nuclei were quantified by computerised densitometry for those volumes of cerebral parenchyma showing Hounsfield numbers that fell within a window set between the two thresholds for leuko-araiosis. To determine the upper and lower threshold values for leuko-araiosis, two of us independently determined the threshold values for Hounsfield units in all subjects and superimposed the densitometric results on the original non-contrast brain images. All independent determinations were in good agreement if the lower threshold for leuko-araiosis was set at 25 Hounsfield units and the upper was set at 34. Areas of leuko-araiosis were expressed as percentage ratios to parenchymal areas at the CT level of basal ganglia. With densitometric methods similar to those described previously, cerebral atrophy was measured as total volumes within the subarachnoid spaces, ventricles, and infarcted brain on the same CT image by utilising values for Hounsfield units below 25 (that is, for cerebrospinal fluid). Results were then expressed as percentage ratios to cerebrospinal fluid volume to intracranial volume (defined as the cerebral atrophic index).

Data are presented as means (SD). Statistical analyses were performed by Student’s two tailed t test. To estimate the relative contributions of reductions of LCBF to the severity of leuko-araiosis, linear multiple regression analyses were performed. The ratios of leuko-araiosis were regarded as the dependent variable and LCBF values for cortical and subcortical grey matter as well as white matter served as explanatory variables. The algorithm used for computation included stepwise entry and removal of the independent variables (F entry and F removal, 2:0).

**Results**

Figure 1 shows measured ratios for frontal leuko-araiosis among patients with dementia compared with age matched normal volunteers. The severity of leuko-araiosis was significantly greater in demented patients than in normal volunteers. No differences were apparent in the severity of leuko-araiosis between patients with MID and those with DAT.

Figure 2 summarises cerebral atrophic indices among demented patients compared with age-matched normal volunteers. Both DAT and MID patients exhibited more cerebral atrophy than normal volunteers. Furthermore, cerebral atrophy among patients with DAT was more severe than among those with MID.

Figure 3 shows a non-contrast CT image of the brain beside the same image with superimposed LCBF values, recorded from a 68 year old man with mild MID. LCBF values were severely reduced in a patchy manner related to numerous lacunar infarcts. Perfusion of the thalamus was decreased bilaterally.

Figure 4 compares LCBF values from nine representative cerebral regions among patients with MID, DAT, and elderly normal volunteers. In patients with MID all LCBF values, except those for parietal white matter, were significantly lower than those in elderly normal volunteers. Likewise, LCBF values were lower for most regions in patients with DAT,
although perfusion in the thalamus was not reduced. There were no significant differences for pooled LCBF values when MID patients were compared with DAT patients, although patchy reductions of LCBF values in infarcted zones were obvious among MID patients, as shown in Fig 3.

Associations of LCBF reductions to severity of frontal leuko-araiosis were assessed by multiple regression analysis (Table 2). Explanatory variables are LCBF values for cortical grey matter, subcortical grey matter, and white matter. Among patients with MID, the coefficient of determination ($R^2$) was 0·582, the coefficient of determination adjusted for the degree of freedom (adjusted $R^2$) was 0·516, and the multiple correlation coefficient was 0·763. Results showed significant correlations between LCBF reductions for subcortical grey matter and severity of leuko-araiosis in MID patients according to analysis of variance ($p < 0·025$, $F$ test). There were no significant correlations between LCBF reductions and frontal leuko-araiosis in DAT patients, nor were there any among age matched normal volunteers.

Concerning the relation between leuko-araiosis and cerebral atrophy, significant correlations between indices for cerebral atrophy (or cerebral parenchymal loss) and ratios for frontal leuko-araiosis were found only in patients with MID (regression equation: percentage of frontal leuko-araiosis = 6·7 + 0·88 × cerebral atrophic indices; $r = 0·57$, $p < 0·005$). Correlations between loss of brain parenchyma and severity of frontal leuko-araiosis in patients with DAT ($r = 0·47$) and in normal volunteers ($r = 0·34$) were not significant.

Partial pressures for end tidal carbon dioxide ($\text{P}_{\text{CO}_2}$) did not differ significantly between elderly normal volunteers (33·6 (4·5) mm Hg), patients with MID (32·0 (2·4), and patients with DAT (31·1 (3·9)). Nor were significant differences found between mean arterial blood pressure values measured among the three groups [normal volunteers, 95·0 (7·6) mm Hg; DAT patients, 95·5 (8·7); MID patients, 97·1 (11·3)]. Alterations in ECG readings were not observed during inhalation of xenon gas in any of the subjects.

Table 2  Multiple regression analyses of LCBF values to severity of frontal leuko-araiosis

<table>
<thead>
<tr>
<th>CBF region studied</th>
<th>Partial regression coefficients</th>
<th>Standardised partial regression coefficients $\text{Normal volunteers}$</th>
<th>Partial correlation coefficients $\text{Multi-infant dementia}$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical grey matter</td>
<td>$-0·017$</td>
<td>$-0·068$</td>
<td>$-0·063$</td>
<td>NS</td>
</tr>
<tr>
<td>Subcortical grey matter</td>
<td>$-0·000$</td>
<td>$-0·004$</td>
<td>$-0·004$</td>
<td>NS</td>
</tr>
<tr>
<td>White matter</td>
<td>$-0·094$</td>
<td>$-0·221$</td>
<td>$-0·209$</td>
<td>NS</td>
</tr>
<tr>
<td>Cortical grey matter</td>
<td>$-0·014$</td>
<td>$-0·040$</td>
<td>$-0·048$</td>
<td>NS</td>
</tr>
<tr>
<td>Subcortical grey matter</td>
<td>$-0·127$</td>
<td>$-0·584$</td>
<td>$-0·529$</td>
<td>NS</td>
</tr>
<tr>
<td>White matter</td>
<td>$-0·164$</td>
<td>$-0·198$</td>
<td>$-0·194$</td>
<td>NS</td>
</tr>
<tr>
<td>Cortical grey matter</td>
<td>$0·256$</td>
<td>$0·426$</td>
<td>$0·365$</td>
<td>NS</td>
</tr>
<tr>
<td>Subcortical grey matter</td>
<td>$0·098$</td>
<td>$0·299$</td>
<td>$0·271$</td>
<td>NS</td>
</tr>
<tr>
<td>White matter</td>
<td>$0·362$</td>
<td>$-0·325$</td>
<td>$-0·262$</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

Associations between the presence of leuko-araiosis and dementia have often been reported. Although the presence of white matter lesions detected by CT or MRI was found to be significantly related to cognitive impairment, these associations were qualitative or semiquantitative. In the present study, volumes of leuko-araiosis were quantitated by objective measurements of the volume of reduced Hounsfield numbers presented in frontal periventricular white matter.

Recently several investigators have used magnetic resonance imaging to evaluate degrees of leuko-araiosis. Although MRI is a powerful instrument for determining white matter lesions, asymptomatic and unexpected lesions are noted which are frequently not detected by CT scanning. The extraordinary sensitivity of MRI often detects trivial white matter lesions without clinical or neuropsychological correlates. These observations agree with results of Herholz et al, who were unable to find any correlations between small white matter lesions detected by MRI and reductions of regional blood flow, although correlations were evident between large white matter lesions and reductions of hemispheric perfusion. The design of the present study permits optimal correlations between severity of leuko-araiosis and reductions of LCBF values since both are measured on the same CT slice.
CT levels selected for measurements included basal ganglia and anterior horns of the lateral ventricles, where leuko-araiosis is most often detected, so that correlations are possible between the severity of frontal leuko-araiosis and perfusion of subcortical structures such as the thalamus and caudate and lentiform nuclei. In addition, in many elderly normal volunteers and MID patients, the LCBF values for parietal cortex and white matter were measured concurrently. Reductions of LCBF values for parietal cortex and white matter were more often present in patients with MID and DAT than in elderly normal subjects, but did not reach statistical significance in parietal white matter, probably because the numbers analysed at this level were too small. The absence of significant reductions in CBF in the thalamus among patients with DAT indicates that in DAT patients the thalamus is relatively well preserved, unlike MID patients. These results are consonant with neuropathological observations as reported by Brun and Englund. 32

Leuko-araiosis was quantified as voxels of white matter having Hounsfield units falling between 34 and 25 in sections 8–10 mm thick, which is an optimal method for quantifying leuko-araiosis according to Hachinski's definition of changes in white matter with "decreased density on CT". 1 It is possible, however, that tissues selected by the CT criteria used as showing leuko-araiosis may include some normal white matter due to partial volume or tissue overlap effects and because some variability exists for Hounsfield unit values in normal white matter.

Despite these limitations of the methods described, more leuko-araiosis was found in patients with MID and DAT than in elderly normal volunteers, which adds quantitative support to previously described qualitative relations of leuko-araiosis and dementia. 7 8 21 31 32 25 27 29 32 Concerning possible relations of leuko-araiosis to the pathogenesis of these two different types of dementia, we were unable to determine differences in degrees of leuko-araiosis among patients with DAT and MID. Erkinjuntti et al and Aharon-Peretz et al concluded that leuko-araiosis was more common and more severe among patients with MID than with DAT. 22 25 Such differences were not observed between DAT and MID patients in this study possibly because our DAT patients were older and more demented than patients with MID.

In patients with MID, decreases in cerebral perfusion supplying the basal ganglia correlate directly with the severity of leuko-araiosis. Clinical and neuropathological correlations suggest that leuko-araiosis may be caused by cerebral hypoperfusion combined with the well known local anatomical vulnerability to ischaemia of white matter surrounding the frontal horns of the lateral ventricles. 7 11 12 31 32 Direct correlations between the severity of leuko-araiosis and hypoperfusion of basal ganglia suggest that ischaemia exists within the territories of the deep cerebral perforating arteries as these vessels supply both periventricular white matter and basal ganglia. Disconnections between cortical grey matter and basal ganglia resulting from leuko-araiosis may exacerbate these local reduced perfusions.

The pathogenesis of white matter lesions causing leuko-araiosis among patients with DAT remains to be determined. As reported by Leys et al, leuko-araiosis in DAT patients may be accounted for, in part, by Wallerian degeneration secondary to neuronal loss. 33 However, Brun and Englund concluded from detailed neuropathological examinations of patients dying with DAT that some white matter lesions were due to ischaemia alone, since arteries supplying abnormal white matter showed "hyaline degeneration" with stenosis and pial and meningeal vessels showed congophilic changes, although immunohemical stains for amyloid were not carried out. 32 These authors also noted that leuko-araiosis in DAT patients occurred independently of the presence of neurofibrillary changes, neuritic plaques, and atrophy of grey matter. Taken together, the results support Hachinski's suggestion that amyloid angiopathy in DAT patients may cause ischaemia of white matter and contribute to leuko-araiosis. 34 This view has been confirmed by immunohemical staining for amyloid in postmortem studies of patients with DAT and among patients with hereditary cerebral infarction and haemorrhage due to amyloidosis of the Dutch type. 32 36 Furthermore, amyloid angiopathy affects the pial vessels more than the deep penetrating arteries.

We concluded that leuko-araiosis of frontal white matter quantified by CT imaging is sometimes present in normal elderly subjects, but is greater in degree among elderly patients with vascular dementia and Alzheimer's
Correlations of leuko-araioisis with cerebral atrophy and perfusion in elderly normal subjects and demented patients

Dementia. In patients with vascular dementia, volumes of leuko-araioisis correlate directly with decreased perfusion of basal ganglia supplied by deep cerebral perforating arteries. Although these observations are compatible with an ischaemic hypothesis for the pathogenesis of leuko-araioisis in MID, the pathogenesis of leuko-araioisis in DAT remains to be established. Amyloid angiopathy may be the key contributor.

Barbara W Clark and Dianne Bailey processed the manuscript. Ada Hindu and James Simon provided technical assistance with CT scanning. This work was supported by a grant from the Department of Veterans Affairs, Central Office, Washington, DC, USA.

Correlations of leuko-araiosis with cerebral atrophy and perfusion in elderly normal subjects and demented patients.

J Kawamura, J S Meyer, M Ichijo, M Kobari, Y Terayama and S Weathers

J Neurol Neurosurg Psychiatry 1993 56: 182-187
doi: 10.1136/jnnp.56.2.182

Updated information and services can be found at:
http://jnnp.bmj.com/content/56/2/182

These include:

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/