White matter magnetic resonance hyperintensities in dementia of the Alzheimer type: morphological and regional cerebral blood flow correlates

Gunhild Waldemar, Pernille Christiansen, Henrik B W Larsson, Peter Høgh, Henning Laursen, Niels A Lassen, Olaf B Paulson

Abstract

In a prospective MRI study the presence, appearance, volume, and regional cerebral blood flow (rCBF) correlates of periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) were examined in 18 patients with probable Alzheimer's disease and in 10 age matched healthy control subjects, all without major cerebrovascular risk factors. The ^{133}Xe inhalation method and the [$^{99\text{m}}\text{Tc}$]-*d,l*-hexamethyl-propylene-amine-oxime (HMPAO) technique with single photon emission computed tomography (SPECT) were used to measure rCBF. Rating scores for PVHs were significantly higher in the Alzheimer's disease group ($p < 0.01$) and correlated significantly with the volume of ventricles ($p < 0.05$) and with systolic arterial blood pressure ($p < 0.01$), but not with rCBF. By contrast, there was no significant difference in the rating scores or volumes of DWMHs between the two groups, although three patients had extensive DWMH lesions in the central white matter. In the group of patients with Alzheimer's disease as a whole, the volume of DWMHs correlated well with rCBF in the hippocampal region ($r = -0.72$; $p < 0.001$), but not with frontal, temporal, parietal, or occipital rCBF. Postmortem histopathology of extensive DWMH lesions in one patient with definite Alzheimer's disease showed a partial loss of myelin and astrocytic gliosis, but no ischaemic changes. It is concluded that DWMH lesions may be associated with reduced rCBF in the hippocampal region. The heterogeneous topography of neocortical rCBF deficits in Alzheimer's disease could not be explained by deafferentation from underlying white matter hyperintensities and therefore may reflect variations in the topography of cortical abnormalities.

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Although the hallmarks of Alzheimer's disease are the plaques and tangles seen in cortical brain tissue on neuropathological examination, Alzheimer's disease is not just a cortical brain disease. Structural involvement of the white matter was suggested in a neuropathological study by Brun and Englund,¹ who showed symmetric deep ischaemic white mat-

ter changes in most of their patients with a definite diagnosis of Alzheimer's disease. Clinical studies measuring the occurrence of white matter abnormalities on MRI in patients with Alzheimer's disease, however, have yielded conflicting results.²⁻⁷

Recently, we described a pronounced topographical heterogeneity of regional cerebral blood flow (rCBF) patterns measured with high resolution single photon emission computed tomography (SPECT) and [$^{99\text{m}}\text{Tc}$]-*d,l*-hexamethyl-propylene-amine-oxime (HMPAO) in patients with a clinical diagnosis of Alzheimer's disease.⁸ A heterogeneity of hypometabolism patterns in Alzheimer's disease was also reported in PET studies.^{9,10} In the absence of vascular pathology, focal deficits in cortical blood flow may reflect either abnormalities in the cortex itself or deafferentation from the underlying white matter. The possible contributions of white matter hyperintensities seen on MRI to the pathogenesis of Alzheimer's disease and to the heterogenous impairments of cognitive function and rCBF remain to be clarified. Also, it is not known whether white matter hyperintensities seen on MRI during the course of the disease have any relation with the histopathological white matter disorder described in neuropathological studies.¹

The aim of this study was to examine the correlation of MRI white matter hyperintensities with rCBF as measured with SPECT and [$^{99\text{m}}\text{Tc}$]-*d,l*-HMPAO. In particular, we aimed to investigate the hypothesis that the presence, topography, or severity of white matter hyperintensities could contribute to the rCBF reduction in the hippocampal regions or to the topographical heterogeneity of rCBF deficits in neocortical brain regions. This report also includes the postmortem neuropathological study in one patient with Alzheimer's disease and with extensive deep white matter hyperintensities on MRI.

Patients and methods

PATIENTS

This prospective study comprised 18 right handed patients who were consecutively referred to the dementia clinic for diagnosis. They fulfilled the DSM-III-R¹¹ criteria for dementia and the National Institute of Neurological Disorder and Stroke and the Alzheimer Disease and Related Disease Association (NINCDS-ADRDA)¹² criteria for probable Alzheimer's disease (table 1). The patients were part of a prospective dementia

Department of
Neurology, University
Hospital,
Rigshospitalet,
Copenhagen,
Denmark
G Waldemar
P Høgh
O B Paulson

Department of
Clinical Physiology,
Bispebjerg Hospital,
Copenhagen,
Denmark
N A Lassen

Magnetic Resonance
Research Center,
Hvidovre Hospital,
Copenhagen,
Denmark
P Christiansen
H B W Larsson

Institute of
Neuropathology,
University of
Copenhagen,
Copenhagen,
Denmark
H Laursen

Correspondence to:
Dr Gunhild Waldemar,
Department of Neurology,
Rigshospitalet, 9,
Blegdamsvej, DK-2100
Copenhagen, Denmark.

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Table 1 Clinical characteristics and MRI data

	Control	Alzheimer's disease	
Clinical data:			
No of subjects (female/male)	10 (4/6)	18 (11/7)	
Age	64 (53-80)	69 (53-78)	NS
Duration of symptoms (y)	—	4 (0.5-10)	
MMSE ¹⁴ score (max 30)	30 (28-30)	17 (3-27)	**
GDS ¹⁵ score (max 7)	—	4 (3-6d)	
Resting arterial blood pressure:			
Systolic	130 (110-160)	140 (95-165)	NS
Diastolic	85 (70-90)	78 (60-95)	NS
MRI data:			
PVH score	0.0 (0-1)	1.5 (0-3)	**
DWMH score	1.0 (0-1)	1.0 (0-3)	NS
Total volume of DWMH (cm ³)	0.07 (0-4.96)	1.04 (0-47.6)	NS
(mean (SD))	(0.79 (1.55))	(5.39 (11.3))	
Total volume of ventricles (cm ³)	24.5 (8.9-56.2)	46.9 (18.6-127.2)	NS
(mean (SD))	(31.1 (17.8))	(54.2 (33.1))	

Values are median (range) unless stated otherwise. Control = healthy control subjects; Alzheimer's disease = patients with a clinical diagnosis of probable Alzheimer's disease; MMSE = mini mental state examination¹⁴; GDS = global deterioration scale¹⁵; PVH = periventricular hyperintensities; DWMH = deep white matter hyperintensities. **p < 0.01, NS = non-significant (patients with Alzheimer's disease v control subjects, Wilcoxon two sample rank sum test).

study reported elsewhere,⁸ and the present report includes only patients in whom a cranial MRI study was available. In one patient (case 04-19), the diagnosis was later confirmed by postmortem neuropathological examination. All patients underwent an extensive study programme to rule out any other disorders that might be associated with dementia, cognitive dysfunction, or altered rCBF.⁸ Briefly, cranial x ray CT was without focal pathology and without periventricular hypodensity in all patients. No patient had a history of psychiatric or neurological disease, except for Alzheimer's disease. All patients had Hamilton¹³ depression scores below or at 10. Cerebrovascular risk factors were minimised: patients with diabetes mellitus, moderate to severe impairment of cardiac or pulmonary function, significant stenosis of the carotid arteries on Doppler examination, chronic arterial hypertension, or increased cholesterol concentrations in the blood were excluded. Resting systolic/diastolic blood pressure was below 180/100 on the study day. The severity of dementia was documented (table 1) by the mini mental state examination (MMSE)¹⁴ and the global deterioration scale (GDS).¹⁵

Ten age matched healthy volunteers, recruited from advertisements, served as a control group for the MRI data (table 1). They had no dementia symptoms or signs, and they met the same exclusion criteria as the patients with Alzheimer's disease. The mapping of significant rCBF deficits in the patients with Alzheimer's disease was based on the rCBF data from a larger control group with 25 healthy control subjects, median age 70 (range 53-83) years.⁸ The patients, with their relatives, and all control subjects gave informed consent to participation in the study, which was approved by the ethics committee of the Cities of Copenhagen and Frederiksberg.

MAGNETIC RESONANCE IMAGING

The MRI study was carried out with a whole body MR scanner (Siemens Magnetom H-15) operating at 1.5 T. The brain was imaged in the axial plane using a double spin echo sequence with repetition time of 1800 ms and an echo time of 30/90 ms. The slice thickness was 4 mm, and the number of slices was 15 with an interslice space of 4 mm. The matrix size was 256 × 256 giving a voxel size of 1.2 × 1.2 × 4 mm³. The interslice spaces left were also imaged.

The images were analysed by two experienced readers of MRI who were not acquainted with the diagnosis of the patients or the rCBF data. Firstly, the readers were asked to rate (in consensus) the presence, shape, and severity of any periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) according to a qualitative scoring method based on the ratings defined by Fazekas *et al*² and Zimmermann *et al*.¹⁶ The PVHs were rated on a 0-4 scale (0 = absent; 1 = discontinuous PVH; 2 = continuous periventricular lining; 3 = continuous periventricular halo; 4 = continuous irregular PVHs). Discontinuous PVHs were defined as rounded hyperintense foci at the angles of the frontal horns, caps of hyperintensity surrounding the occipital horns, and

Table 2 Magnetic resonance hyperintensities and rCBF deficits in patients with probable Alzheimer's disease

Case	PVH score	DWMH score	DWMH volume (cm ³)				Cortical rCBF deficits	
			Total	Central white matter	Left lobar white matter	Right lobar white matter	Left	Right
01-02	2	0	0	0	0	0	T, P	F, T, P
02-09	0	1	2.08	2.08	0	0	—	F
03-17	2	1	0.68	0.68	0	0	F, T	F
04-19	1	2	15.20	15.20	0	0	T	F, T, P, OC
05-21	1	1	10.04	9.24	0.48 (F + OC)	0.32 (F)	—	F, T
06-23	1	1	4.52	4.40	0	0.12 (P)	T, P, OC	T, P
07-26	1	1	3.50	3.48	0.02 (OC)	0	F, P	F
08-32	0	0	0	0	0	0	F, T, P, OC	—
09-33	2	1	4.52	1.96	1.40 (OC)	1.16 (OC)	T	F, T
10-34	0	1	0.92	0.56	0.28 (OC)	0.08 (OC)	F	—
11-37	2	1	0.10	0.10	0	0	F, T, P	F
12-41	3	3	47.62	47.62	0	0	F, T, P	—
13-43	2	1	0.64	0.64	0	0	—	T, P
14-44	3	1	1.16	1.16	0	0	—	OC
15-47	2	1	0.44	0.28	0	0.16 (F)	—	P
16-51	1	1	5.12	5.12	0	0	T, P	—
17-52	2	2	0.40	0.40	0	0	T, P	F, T, P
18-53	0	0	0	0	0	0	T	F, T, P

rCBF = Regional cerebral blood flow; PVH = periventricular hyperintensities; DWMH = deep white matter hyperintensities; F = frontal cortex; T = temporal cortex; P = parietal cortex; OC = occipital cortex.

Table 3 Correlation coefficients for white matter magnetic resonance hyperintensities v clinical data and rCBF in patients with probable Alzheimer's disease (n = 18)

	PVH score	DWMH score	DWMH volume
Age	0.46	0.52†	0.29
Age at onset	0.45	0.44	0.30
Duration of symptoms	-0.07	-0.22	0.23
Resting arterial blood pressure:			
Systolic	0.76††	0.48†	0.23
Diastolic	0.47	0.46	0.28
MRI data:			
PVH score	NR	0.51†	0.44
DWMH score	0.51†	NR	0.76***
DWMH volume	0.11	-0.76††	NR
Volume of ventricles	0.52†	0.38	0.47*
MMSE score	-0.17	0.25	0.20
Cerebral blood flow (a/b):			
Global CBF	-0.34/-0.35	-0.29/-0.14	-0.52/-0.24
rCBF			
Frontal cortex	-0.38/-0.36	-0.31/-0.10	-0.42/-0.30
Temporal cortex	-0.29/-0.27	-0.26/-0.09	-0.46/-0.18
Parietal cortex	-0.32/-0.24	-0.24/-0.06	-0.27/-0.24
Occipital cortex	-0.41/-0.34	-0.32/-0.14	-0.30/-0.26
Hippocampal region	-0.15/NA	-0.22/NA	-0.72***NA
Central white matter	-0.42/NA	-0.28/NA	-0.56*/NA

*p < 0.05; ***p < 0.001 (Pearson product-moment correlations).

†p < 0.05; ††p < 0.01 (Spearman rank order correlations).

a/b = correlation coefficients; these are shown for rCBF data obtained with both CBF methods (^{99m}Tc -d,l-HMPAO(a)/ ^{133}Xe inhalation (b)); PVH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities; MMSE = mini mental state examination score; NA = not available; NR = not relevant.

streaks of hyperintensity extending along the atria of the lateral ventricles. Continuous irregular PVHs were defined as PVHs extending from the ventricular lining into the deep white matter to the corticomedullary junction involving most of the white matter, the lateral margins of the hyperintensity being irregular. Separate white matter signal hyperintensities that were not confluent with the ventricular lining were rated as DWMHs on a 0–3 scale ((0 = absent): 1 = punctuate (solitary) foci; 2 = beginning of confluence of foci; 3 = large confluent areas). Next, the readers measured the volume of all DWMH elements in: (a) the central white matter in the frontal and occipital regions and parallel to the lateral ventricles, including all white matter tissue within the corticomedullary junction; (b) lobar white matter separately in the left and right frontal, temporal, parietal, and occipital regions. These regions were defined on templates constructed before the study with reference to axial brain slices from an anatomical brain atlas.¹⁷ Each hyperintensity lesion was encircled with a cursor on the computer screen, and the area was calculated automatically. The slice volume of each lesion was estimated by multiplying by the voxel volume. The total volume of the hyperintensities was calculated by adding together the volume of all lesions on all slices. The total volume of the ventricles was measured by a similar procedure.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Firstly, rCBF was measured by the ^{133}Xe inhalation technique with a Tomomatic 64 (Medimatic, Hellerup, Denmark), a rapidly rotating and highly sensitive brain dedicated three slice instrument for brain SPECT described elsewhere.¹⁸ The ^{133}Xe inhalation study was performed to obtain absolute measures for CBF. From this study global CBF and rCBF in the cerebellum and in the frontal, temporal, parietal, and occipital cortex were calculated. Methods for calculation

of CBF and regional data analysis have been described elsewhere.^{18–20} Subsequently, rCBF was measured semiquantitatively by static imaging of the distribution of an intravenous dose (1.1 GBq) of [^{99m}Tc]-d,l-HMPAO (Exametazime, Ceretec, Amersham, London, UK). The imaging protocol and the analysis of rCBF data have been described elsewhere.^{8,20} Briefly, the count rates from nine contiguous image slices covering the whole brain were corrected to adjust for the initial preferential back diffusion of the tracer from high flow regions by the algorithm suggested by Lassen *et al.*,²¹ with a conversion to clearance ratio of 1.5. The cerebellar hemisphere with the highest count rate was used as the reference region. Mean rCBF was calculated in the hippocampal regions and in frontal, temporal, parietal, and occipital cortical regions of interest.^{8,20,22} The side to side asymmetry index was defined as the difference between rCBF values in the right and the left counterparts of the region of interest, relative to the higher of the two values. Two anterior:posterior ratios were defined as the ratio of mean rCBF in the frontal cortex to mean rCBF in the temporal cortex or the parietal cortex, respectively.²⁰ Based on the rCBF data from a large control group,⁸ the regions of interest with significant rCBF deficits were mapped for each patient. In each region of interest rCBF was considered reduced if the relevant side to side asymmetry index or anterior:posterior ratio of rCBF was significantly abnormal (deviating more than 2 SD from the control mean), or if the mean rCBF value was severely reduced, by more than 3 SD from the control mean.⁸

CORRELATIONS BETWEEN MRI

HYPERINTENSITIES, CLINICAL DATA, AND rCBF
The rating scores for PVHs and DWMHs and the quantitative volume measurements of DWMHs were compared in the two groups. Within the group of patients with Alzheimer's disease a correlation analysis was carried out for the PVH and DWMH rating scores and for the volume of DWMHs v age, MMSE score, age of disease onset, duration of symptoms, resting systolic and diastolic arterial blood pressure, volume of ventricles, and global as well as rCBF. A correlation analysis was also performed for the side to side asymmetry of the global DWMH volume v that of global CBF. Finally, the MRI variables were compared in the groups of patients with and without frontal hypoperfusion and, when relevant, the rCBF patterns were examined for rCBF deficits in the cortical regions of interest adjacent to any lobar DWMH lesions.

STATISTICAL METHODS

The Wilcoxon two sample rank sum test was used for intergroup comparisons of data. The possible relations between the quantitative DWMH volume measurements and other variables were analysed by Pearson product moment correlations. Correlations concerning the qualitative rating scores for PVHs and DWMHs were analysed by the Spearman rank order analysis. A Bonferroni correction

was applied to the p values for differences in rCBF data.⁸ For all statistical tests the minimal level of significance was $p < 0.05$.

Results

MAGNETIC RESONANCE IMAGING

The rating scores for PVHs were significantly ($p < 0.01$) higher in the Alzheimer's disease group than in the controls (table 1). By contrast, there was no significant difference in the rating scores or volume measurements of DWMHs between the two groups (table 1). In all control subjects and in most patients

with Alzheimer's disease the total volume of DWMHs was below 5 cm³, and more than 95% of the total DWMH volume was located in the central white matter (tables 1 and 2). In three patients with Alzheimer's disease (cases No 04–19, 05–21, and 12–41), however, the total volume of DWMHs was very high, exceeding by far the maximal DWMH volume in the control group.

SINGLE PROTON EMISSION COMPUTED TOMOGRAPHY

Global CBF measured with the [^{99m}Tc]-d,l-HMPAO method (normalised to the cerebellum) was 85.2 (SD 7.9)% in the control group and 75.2 (9.6)% in the Alzheimer's disease group ($p < 0.01$). There was a significant ($p < 0.01$) reduction of rCBF in the frontal, temporal, and parietal cortexes, and in the hippocampal regions, whereas the occipital cortex and the subcortical grey matter regions were spared.⁸ The individual rCBF patterns have been described elsewhere⁸ and table 2 summarises these. All patients had an abnormal rCBF pattern. A pronounced topographical heterogeneity of rCBF patterns for the number of affected regions, laterality, and anterior posterior asymmetry, was found. There was no significant difference between the two groups in cerebellar blood flow as measured with the ¹³³Xe inhalation technique.

CORRELATIONS BETWEEN MRI HYPERINTENSITIES AND CLINICAL DATA

Within the group of patients with Alzheimer's disease the DWMH but not the PVH rating scores correlated significantly with age. The PVH scores and the DWMH volumes correlated significantly with the volume of the ventricles (table 3). There was no significant difference in any of the MRI variables between patients with presenile and senile onset of symptoms. The PVH scores correlated significantly with resting systolic arterial blood pressure ($r = 0.76$; $p < 0.01$). Likewise, there was a slight, but significant, correlation between the DWMH scores and systolic arterial blood pressure ($r = 0.48$; $p < 0.05$). None of the MRI variables correlated with age at onset, duration of symptoms, diastolic arterial blood pressure, or cognitive performance as measured with the MMSE score.

CORRELATIONS BETWEEN MRI HYPERINTENSITIES AND rCBF

The DWMH volumes correlated significantly with rCBF in the central white matter ($r = -0.56$; $p < 0.05$), and remarkably well with rCBF in the hippocampal region ($r = -0.72$; $p < 0.001$), but not with rCBF in any of the four major cortical regions (table 3). Accordingly, there was no significant correlation between the side to side asymmetry of the DWMH volume and that of cortical rCBF, and there was no significant difference in any of the MRI variables between patients with and without frontal hypoperfusion. Only two of the six patients with small DWMH lesions

Figure 1 MRI images (top) and [^{99m}Tc]-d,l-HMPAO SPECT images (bottom) from a 72 year old female patient with a diagnosis of definite Alzheimer's disease verified by neuropathological examination at necropsy (case 04–19). The left hemisphere is shown to the left. In the SPECT images the colour scale indicates rCBF (normalised to the cerebellum). This patient presented with presenile onset of progressive dementia, fulfilling the clinical criteria for probable Alzheimer's disease. The MMSE score was 15, and the GDS (global deterioration scale) score was 5. There was no history of cerebrovascular risk factors. In the neuropsychological examination memory, language, visual perception, and visuoconstruction were significantly impaired. On MRI (top) a moderate and diffuse cortical atrophy was seen, the PVH score was 1, and the DWMH score was 2. Extensive DWMH lesions, with a total volume of 15.2 cm³, were located symmetrically in the central white matter. The SPECT study (bottom) showed asymmetric focal rCBF deficits in the temporoparietal regions and in the right frontal cortex. The symptoms and SPECT abnormalities continued to progress, still with no clinical signs of vascular brain disorder. Fig 2 shows the postmortem neuropathological examination obtained three years later.

Figure 2 Histological tissue preparations showing white matter lesions in patient 04–19 (for case history see fig 1). (A) Macroscopically identified white matter lesion. Myelin stain shows extensive demyelination. Klüver-Barrera stain (bar 180 µm). (B) Same lesion as in A. Tissue heavily infiltrated by macrophages. Haematoxylin-eosin stain (bar 70 µm). (C) Macroscopically unidentified white matter lesion. Myelin stain demonstrates pallor and oedematous dispersion of myelinated tracts, but no demyelination. Klüver-Barrera stain (bar 70 µm). (D) Same lesion as in C. Astrocytes are swollen with distorted outlines. Glial fibrillary acid protein immunostain (bar 30 µm).

in the lobar white matter had rCBF deficits in one of the relevant adjacent cortical regions (table 2). No significant correlations were found between the qualitative rating scores for PVHs and DWMHs and rCBF. The topography of cortical rCBF deficits in the rCBF patterns could not be subtyped according to the presence or severity of white matter lesions (table 2). In particular, the cortical rCBF patterns of the three patients with extensive DWMH lesions did not differ from those of the other patients.

NEUROPATHOLOGY

In one of the patients (case 04–19) with extensive DWMH lesions a postmortem neuropathological examination was obtained (figs 1 and 2). Abundant plaques and tangles were seen in all cortical brain regions. Only very few of the deep white matter lesions on MRI could be identified macroscopically. Tissue blocks taken from these areas and from periventricular areas with well defined MRI lesions were examined histologically (fig 2).

Some of the lesions were easily identified as small areas of demyelination infiltrated with macrophages and with astrocytosis. In other lesions, the only obvious change was astrocytosis identified by increased immunoreactivity in glial fibrillary acid protein immunohistochemical stains. In some of these lesions a slight pallor in the myelin stain suggested oedematous dispersion of fibre tracts, but obvious demyelination was not present. In all lesions hyalinised blood vessels were present, but complete obstruction or thrombosis was not found.

Discussion

The highly significant correlation between the volume of DWMHs and hypoperfusion in the hippocampal regions suggested that DWMHs may be a marker for the severity of dysfunction or atrophy in medial temporal lobe structures. This study also showed that white matter hyperintensities could not explain the characteristic topographical heterogeneity of focal cortical rCBF deficits in dementia of the

Alzheimer type. Therefore, the heterogeneity must reflect variations in the topography of cortical pathology. We used an MRI scoring method that distinguished between PVHs and DWMHs, because histological and epidemiological studies have suggested a different aetiology for these categories of white matter lesions.^{2,3,23,24} The inter-rater reliability of the scoring method has been shown to be very high,⁵ and in our study the qualitative estimation of DWMHs was refined by quantitative volumetric measurements.

The PVH foci just anterior to the frontal horns probably do not reflect pathology. They are thought to be caused by an age related loss of ependyma leading to increased water content.²³ Thus if a PVH score greater than 1 is abnormal, then abnormal PVHs (continuous PVHs along the side of the ventricles) were seen in 50% of our patients with Alzheimer's disease but not in any of the healthy subjects. The PVH scores correlated significantly with systolic arterial blood pressure, but differences in blood pressure could not explain the differences in PVHs between the two groups. The low frequency of PVHs in our group of healthy subjects without major cerebrovascular risk factors corresponds to that reported by Fazekas *et al.*²⁵ The increased frequency and extension of PVHs in patients with Alzheimer's disease, which suggested that PVHs may be associated with the Alzheimer's disease process, is in agreement with the findings of McDonald *et al.*²⁶ By contrast, Leys *et al.*,⁶ Kozachuk *et al.*,⁵ and Fazekas *et al.*²⁷ failed to find any difference in PVHs between patients with Alzheimer's disease and healthy subjects. Scheltens *et al.*⁷ found increased severity of PVHs in his group of patients with Alzheimer's disease and with senile onset of disease, but not in presenile onset Alzheimer's disease. We were unable to show any association between the severity of PVHs and age of onset or duration of symptoms. Thus whereas our data on the presence of PVHs in Alzheimer's disease confirmed the results of some, but not all, previous reports, the important finding was that although PVHs were significantly associated with the diagnosis of Alzheimer's disease PVHs were not a determining factor for the cortical rCBF deficits or for global cognitive performance.

By contrast with PVHs the rating scores and volumes of DWMHs were not higher in the group of patients with Alzheimer's disease as a whole. Solitary foci of DWMHs were seen in 70% of our control subjects, a high frequency that corresponds with that reported by Fazekas *et al.*²⁵ The lack of difference in DWMH scores between patients with Alzheimer's disease and normal subjects was in agreement with the findings of some previous reports,^{2,4-6,28} but contradicted others.^{3,29-33} It is well known that the presence of cerebrovascular risk factors increases the risk of DWMHs,^{25,26,34} and Scheltens *et al.*⁷ suggested that DWMHs may be more prevalent in patients with senile onset of Alzheimer's disease than in patients with presenile onset, even when cerebrovascular risk factors have

been controlled. In previous studies only subjective rating methods have been applied. By inclusion of volumetric measurements of DWMHs, our study confirmed that when cerebrovascular risk factors have been controlled, the clinical diagnosis of probable Alzheimer's disease is not likely associated with increased DWMHs. Within the group of patients with Alzheimer's disease, however, there was a high variation in the volumetric data, and three patients had extensive DWMH lesions, suggesting a heterogeneity in the presence and severity of DWMHs. A very high variation in DWMH volume measurements was also reported by others.³⁵ Furthermore, the highly significant negative correlation with blood flow in the hippocampal regions points to a possible pathophysiological link between DWMHs and the degenerative process of Alzheimer's disease, at least in some patients.

Three questions remain unanswered. Firstly, could DWMHs be part of the Alzheimer's disease process in selected patients? Secondly, if DWMHs on MRI are not associated with Alzheimer's disease, then what are the clinical correlates of the histological white matter lesions that have been described in 60% of patients with Alzheimer's disease at necropsy? Brun and Englund suggested that these abnormalities were due to hypoperfusion of the concerned white matter territories, but no information from MRI was available in their study.¹ Thirdly, what are the morphological correlates of the DWMH lesions seen on MRI in healthy subjects as well as in patients with Alzheimer's disease? The literature on histopathological examination of MRI white matter lesions in Alzheimer's disease is sparse: in a preliminary postmortem report on three patients with definite Alzheimer's disease Morris *et al.*³⁶ found increased water content, but no histological lesions, in regions with "periventricular high signals". Whether these high signals represented deep white matter hyperintensities or periventricular hyperintensities was not defined in their report, and the vessels were not described. We were able to perform a postmortem neuropathological examination of the brain from one of our patients with definite Alzheimer's disease and extensive DWMH lesions on MRI. The partial loss of myelin and astrocytic gliosis, which was seen in the white matter regions corresponding to those containing DWMHs on MRI, resembled some of the abnormalities described in the necropsy studies by Brun and Englund in patients with Alzheimer's disease.¹ Similar histopathological changes were found, however, by Fazekas *et al.*²⁴ in healthy subjects with DWMHs on MRI. In our patient hyalinised blood vessels were found in the central white matter, but they were not associated with vessel occlusion or ischaemic changes. Thus perivascular damage could not be proved to be the substrate of the DWMHs. We suggest that neither the DWMHs on MRI nor the histological white matter findings in our patient were related to the Alzheimer's

disease process. Most likely DWMHs seen on MRI are related to normal aging, cerebrovascular risk factors, and chronic cerebrovascular disease,³⁷ rather than to the Alzheimer's disease process. The prevalent histological white matter disorder described by Brun and Englund¹ in Alzheimer's disease as well as our finding of a significant correlation between the volume of DWMHs and hypoperfusion in the hippocampal regions, however, support the hypothesis of a pathophysiological link between DWMHs and Alzheimer's disease.

The DWMHs did not contribute to the characteristic cortical rCBF deficits in Alzheimer's disease. The finding was confirmed with the ¹³³Xe inhalation method as well as with the [^{99m}Tc]-d,l-HMPAO technique for measuring rCBF. In accordance with this, measurements of glucose metabolism with PET have failed to show hypometabolism of cortical areas adjacent to white matter hyperintensities.²⁸ Although none of our patients had chronic arterial hypertension, the significant correlation between the severity of PVHs (and to some extent also DWMHs) and systolic arterial blood pressure supports the hypothesis that arterial blood pressure may be an aetiological factor for white matter hyperintensities.

In conclusion, clinically diagnosed Alzheimer's disease without major cerebrovascular risk factors was associated with an increased frequency and severity of PVHs. There was no relation, however, between the presence of PVHs and global cognitive performance or the rCBF patterns. By contrast, DWMHs were not significantly associated with the diagnosis of Alzheimer's disease. The histopathology of extensive DWMH lesions in one patient with Alzheimer's disease included partial loss of myelin and astrogliosis, changes that were not different from those described in normal subjects with DWMHs. Within the group of patients with Alzheimer's disease, however, the variation in DWMH volumes was high, and the total volume of DWMHs correlated significantly with the reduction of rCBF in the hippocampal regions, suggesting a pathophysiological link between DWMHs and Alzheimer's disease. The characteristic and heterogeneous topography of focal cortical rCBF deficits in probable Alzheimer's disease could not be explained by deafferentation from white matter hyperintensities and therefore must reflect variations in the topography of cortical abnormalities.

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NEUROLOGICAL STAMP

Dorothea Lynde Dix (1802-87)

Dorothea Dix came from New England. Here she noticed the horrible conditions in an asylum. Some warders made a small charge for visitors to come and look at the mad and prod them into raving antics. In 1841 she laid before the Massachusetts General Assembly a description of the insane in jails and private institutions. She spent the rest of her life fighting to improve conditions of the insane.

Anton Ashley Cooper, afterwards Lord Shaftesbury, had discovered similar problems in England 10 years earlier while sitting on a Royal Commission to investigate such conditions. The lunatics at Bedlam were long regarded as one of the sights of London.

Miss Dix travelled thousands of miles by stagecoach, steamboat, and on horseback and quietly collected facts, which she recorded in sober restrained prose. She possessed great charm and a commanding voice. With these attributes, facts collected from a comprehensive study of asylums, and a selection of public speakers to sustain protest she harassed officials and influenced legislatures.

In 1843, in the face of her continuing investigation and increasing community agitation, the Massachusetts Legislature passed a Bill providing for adequate hospitalisation of the insane. This was her first triumph. She became an effective lobbyist in many of the States and a national figure. Her work and influence also led to improvement of the conditions of the insane in Great Britain—and also in Italy after an audience with the Pope. She travelled in Europe and crusaded for human rights of patients until her death at the age of 85.

The centennial of her death, 1987, went largely unnoticed but in 1980 a United States postage stamp had commemorated the first woman who brought the plight of the mentally ill into such prominence (Stanley Gibbons 1818, Scott 1844).

L F HAAS