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WHITE MATTER LESIONS ON MAGNETIC RESONANCE IMAGING IN CLINICALLY DIAGNOSED ALZHEIMER'S DISEASE

EVIDENCE FOR HETEROGENEITY

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SUMMARY

In a prospective magnetic resonance imaging (MRI) study we evaluted the prevalence and severity of white matter changes in 29 patients with Alzheimer's Disease (AD) and 24 age-matched healthy elderly, all without cerebrovascular risk factors.

The AD patients were divided into two groups according to age at onset of symptoms, one with presenile onset AD (n = 13) and one with senile onset AD (n = 16), who were matched for dementia severity. Signal hyperintensities were rated using a semiquantative scoring method, separately in the periventricular region (PVH) and in the lobar white matter (WMH), as well as in the basal ganglia (BGH) and in the infratentorial region (ITFH). Cortical atrophy as a parameter of grey matter involvement was rated on a 0 (absent) to 3 (severe) scale.

We found PVH, WMH and BGH scores to be significantly higher in senile onset AD patients than in age-matched controls. By means of multiple linear logistic regression we found that PVH, WMH and BGH scores were significantly dependent on the diagnosis of senile onset AD, while the PVH score also showed a significant age dependency. Cortical atrophy did not differ significantly between presenile onset AD and senile onset AD patients.

These results indicate that presenile onset AD and senile onset AD patients differ with respect to white matter involvement, but not with respect to grey matter involvement on MRI. Since cerebrovascular risk factors were excluded these findings may indicate that senile onset AD patients display more small vessel involvement (arteriolosclerosis) than presenile onset AD patients, suggesting additional (microvascular) factors for the dementia syndrome in senile onset AD. Our data lend support to the growing body of evidence that AD is heterogeneous, consisting of at least two types. Based on our findings two forms can be distinguished: (i) a 'pure' form of the disease, usually with early disease onset, and no more white matter changes than normal for age; (ii) a 'mixed' form, usually with disease onset later in life, and showing more white matter changes on MRI than normal for age.

INTRODUCTION

Alzheimer's Disease (AD) is a degenerative disease characterized by cerebral atrophy with cortical and subcortical grey matter changes. Brun and Englund (1986), however, found symmetrical deep white matter changes at autopsy in more than 60% of patients

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with AD. Histopathologically these changes consisted of a partial loss of myelin, oligodendroglial cells and axons and mild reactive gliosis, in the absence of hypertensive vascular changes. They postulated that these changes were of cerebrovascular hypoperfusional/hypoxic origin (Englund *et al.*, 1988).

White matter changes in patients with dementia were recognized on computerized tomography (CT) (Erkinjuntti *et al.*, 1984; Rezek *et al.*, 1987) and were termed 'leuko-araiosis' (Hachinski *et al.*, 1987). They were also seen on magnetic resonance imaging (MRI) (Fazekas *et al.*, 1987; Johnson *et al.*, 1987). In general, they were often interpreted as being diagnostic for vascular dementia, in particular Binswanger's disease (Erkinjuntti *et al.*, 1984; Hershey *et al.*, 1987). However, white matter abnormalities were increasingly reported in AD too, but studies regarding the actual occurrence of white matter lesions in AD have yielded conflicting results. For instance, Fazekas *et al.* (1987), Rezek *et al.* (1987), Erkinjuntti *et al.* (1989), Kertesz *et al.* (1990) and Leys *et al.* (1991) found significantly more white matter changes in AD patients than in healthy controls, whereas Leys *et al.* (1990) and Kozachuk *et al.* (1990) failed to find any difference in white matter changes between these groups. The contribution of white matter changes to the clinical features of the dementia syndrome in AD is also still under debate (Gupta *et al.*, 1988; Rao *et al.*, 1989; Bondareff *et al.*, 1990; Kertesz *et al.*, 1990).

The differences in prevalence ranges can partly be explained by the use of different imaging modalities but we propose two other possible explanations. First, in most of the MRI studies the presence and severity of white matter hyperintensities were assessed by means of the Fazekas' rating scale (Fazekas *et al.*, 1987). This scale provides only global information contrary to the CT method of scoring leuko-araiosis (Rezek *et al.*, 1987). In addition, inter-observer reliability of the Fazekas method has been shown to be poor (Leys *et al.*, 1990, 1991). Secondly, in most of the imaging studies AD was considered to be one single disease entity. However, clinical, biochemical and neuroimaging studies have shown differences between presenile onset AD and senile onset AD (Gottfries *et al.*, 1983, 1985; Rossor *et al.*, 1984; Wallin *et al.*, 1989; Blennow *et al.*, 1991). If the prevalence of white matter lesions differs between these subtypes of AD, this could explain the contradictory results of earlier studies. If substantiated, the combination of different clinical manifestations and different MRI findings would support the idea that presenile and senile AD are different disease entities and therefore require a different scientific approach and different therapeutic strategies (Gottfries, 1989*b*; Roth and Wischnik, 1985).

In this prospective study we investigated the prevalence and severity of white matter involvement in patients with early- and late-onset AD, who were matched for severity of dementia, using a newly developed semiquantitative rating scale. We also evaluated grey matter involvement by assessing cortical atrophy in both groups. Since white matter lesions are reported to be correlated with cerebrovascular risk factors and age (Awad *et al.*, 1986; Gerard and Weisberg, 1986), we used age-matched healthy elderly people for comparison, and we included only patients and controls without cerebrovascular risk factors.

SUBJECTS AND METHODS

Patients

Twenty-nine AD patients were included in the study. The diagnosis of probable AD was established according to the National Institute of Neurologial Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984). To minimize the influence of cerebrovascular risk factors, we did not include patients with a history or signs and symptoms of cardiac disease. In addition, patients whose systolic blood pressure had ever been found to be higher than 140 mmHg, or whose diastolic blood pressure had been higher than 90 mmHg were not included. Fasting glucose blood levels had to be lower than 5.6 mmol/l and Hachinski's Ischaemic score had to be lower than, or equal to, 4 (Hachinski *et al.*, 1975). Laboratory studies, including serum chemistry testing, a complete blood cell count and differential cell count, vitamin B_{12} and folic acid levels and urin analysis, had to be normal. Finally, a CT-scan was made to exclude cerebral infarcts and other intracerebral pathology. None of the included patients had a conclusive family history of AD, and none of them displayed myoclonus or extra-pyramidal signs. Histopathological confirmation of the clinical diagnosis AD was obtained in four patients.

According to the age at onset of symptoms (determined by comprehensive discussions with carers and spouses) the AD patients were divided into two groups: 13 with presenile dementia of Alzheimer type (presenile onset AD) and 16 patients with senile dementia of Alzheimer type (senile onset AD), with the demarcation at 65 yrs, in agreement with the NINCDS-ADRDA criteria. Severity of dementia was measured by means of the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975). There was no statistically significant difference in MMSE scores between presenile onset AD and senile onset AD patients (one-way ANOVA).

Controls

The control group consisted of 24 healthy volunteers. Some were enrolled from a project on 'successful aging' organized by the University, others were patients suffering from non-neurological disease, or relatives of the investigators, and one was the twin sister of a patient. Each of them had given informed consent after the nature of the procedure had been fully explained. Their selection depended upon the absence of the following criteria: positive family history of dementia; a history of brain disease or psychiatric disease; history or signs and symptoms of cerebrovascular disease, including arterial hypertension; use of any medication; an MMSE score below 27. They underwent the same clinical evaluation as the patient group, with the exception of a CT scan of the brain.

The controls were divided into two subgroups to match the presenile onset AD and senile onset AD groups in age, Norm 1 (n = 14) and Norm 2 (n = 10), respectively. The characteristics of patients and controls are given in Table 1. Statistical analysis failed to reveal any difference between the presenile onset AD and Norm 1 group, and between the senile onset AD and Norm 2 group, for (one-way ANOVA), and for mean blood pressure and mean blood glucose levels between the four groups (Kruskall-Wallis analysis of variance).

TABLE 1. SUBJECT CHARACTERISTICS

	Presenile onset AD group	*Control group Norm 1*	*Senile onset AD group*	*Control group Norm 2*
n	13	14	16	10
F/M	9/4	7/7	8/8	6/4
Age (years) ± SD (Range years)	62.4 ± 6.5 (52 – 69)	63.8 ± 4.7 (54 – 69)	75.1 ± 3.8 (68 – 81)	73.9 ± 2.9 (70 – 80)
MMSE scores (Range)	13.2 ± 5.7 (5 – 23)	29.2 ± 1.0 (27 – 30)	15.0 ± 4.6 (6 – 21)	28.1 ± 0.9 (27 – 30)

Methods

Magnetic resonance imaging was performed on a 0.6 T Teslacon superconducting magnet using multi-slice/multi-echo SE technique, with two excitations and a 1.6 × 1 mm in plane resolution. We used mildly T_2-weighted (TR 2500 ms, TE 60 and 120 ms) axial slices, with a slice thickness of 7.5 mm and a 25% interslice gap, and no flow compensation.

Signal hyperintensities were defined (at TE 60) as areas of higher signal intensity compared with brain tissue and cerebrospinal fluid, which have intermediate signal intensity at this TE, and were scored in

a semiquantitative way. This scoring method produces a score related to both the size and number of foci with increased signal hyperintensity. Signal hyperintensities were scored in the following regions: (i) periventricular, in the frontal and occipital region and parallel to the lateral ventricles; (ii) lobar white matter, separately in the frontal, temporal, parietal and occipital region; (iii) the basal ganglia: caudate nucleus, putamen, globus palidus and thalamus; (iv) the infratentorial region: cerebellum, mesencephalon, pons and medulla. Scores of different brain regions were added to obtain the following sum scores: periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities (BGH) and infratentorial foci of hyperintensity (ITFH). Involvement of the subcortical U-fibres was noted as present or absent. The method is shown in detail in Table 2. Examples of different scores are given in Fig. 1A–G.

TABLE 2. VISUAL RATING OF MRI HYPERINTENSE LESIONS

Periventricular hyperintensities			
Caps:	Occipital	0/1/2	0 = absent
	Frontal	0/1/2	1 = ≤5 mm
			2 = ≥6 mm and ≤10 mm
Bands:	Lateral ventricles	0/1/2	
		PVH =	
White matter hyperintensities			
	Frontal	0/1/2/3/4/5/6	0 = no abnormalities
	Parietal	0/1/2/3/4/5/6	1 = ≤3 mm; n ≤ 5
	Occipital	0/1/2/3/4/5/6	2 = ≤3 mm; n ≥ 6
	Temporal	0/1/2/3/4/5/6	3 = 4–10 mm; n ≤ 5
		WMH =	4 = 4–10 mm; n ≥ 6
			5 = ≥11 mm; n ≥ 1
			6 = confluent
Basal ganglia hyperintensities			
	Caudate nucleus	0/1/2/3/4/5/6	
	Putamen	0/1/2/3/4/5/6	
	Globus pallidus	0/1/2/3/4/5/6	
	Thalamus	0/1/2/3/4/5/6	
		BGH =	
Infra-tentorial foci of hyperintensity			
	Cerebellum	0/1/2/3/4/5/6	
	Mesencephalon	0/1/2/3/4/5/6	
	Pons	0/1/2/3/4/5/6	
	Medulla	0/1/2/3/4/5/6	
		ITFH =	

Cortical atrophy was rated (at TE 120) on a scale ranging from 0 (no atrophy) to 3 (severe atrophy) separately in the frontal, temporal, parietal and occipital regions. Magnetic resonance imaging scans were viewed by two experienced raters and scored according to the criteria outlined above when consensus was reached. Both viewers were blinded to the age and diagnosis of the subject.

Statistical assessment

Differences in the hyperintensity scores and cortical atrophy ratings were tested using the non-parametric Mann-Whitney U test. Multiple linear regression analysis was performd using a model including age and two so-called indicator variables, one for each dementia category, to establish the influence of these variables on the PVH, WMH and BGH scores. Data were analysed using the SPSS/PC™ statistical package. *P*-values <0.05 were regarded as statistically significant. Null hypotheses were tested two sided.

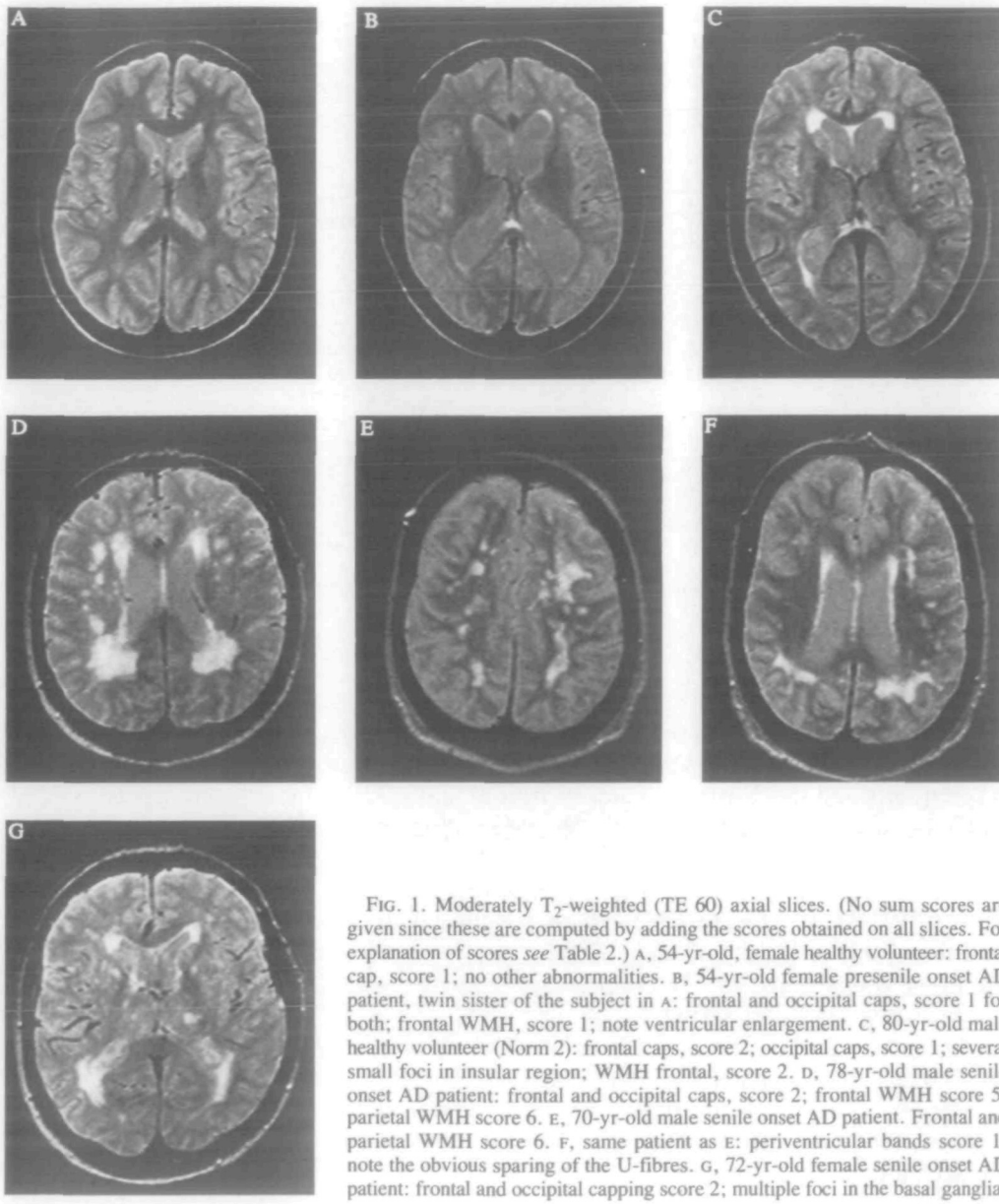

FIG. 1. Moderately T_2-weighted (TE 60) axial slices. (No sum scores are given since these are computed by adding the scores obtained on all slices. For explanation of scores *see* Table 2.) A, 54-yr-old, female healthy volunteer: frontal cap, score 1; no other abnormalities. B, 54-yr-old female presenile onset AD patient, twin sister of the subject in A: frontal and occipital caps, score 1 for both; frontal WMH, score 1; note ventricular enlargement. C, 80-yr-old male healthy volunteer (Norm 2): frontal caps, score 2; occipital caps, score 1; several small foci in insular region; WMH frontal, score 2. D, 78-yr-old male senile onset AD patient: frontal and occipital caps, score 2; frontal WMH score 5; parietal WMH score 6. E, 70-yr-old male senile onset AD patient. Frontal and parietal WMH score 6. F, same patient as E: periventricular bands score 1; note the obvious sparing of the U-fibres. G, 72-yr-old female senile onset AD patient: frontal and occipital capping score 2; multiple foci in the basal ganglia.

RESULTS

The MRI findings are summarized in Table 3. None of the images showed involvement of the subcortical U fibres. We found no significant differences in any of the hyperintensity scores between presenile onset AD patients and the Norm 1 group.

Statistically significant differences in the scores for the occipital caps, the bands adjacent

TABLE 3. SUMMARY OF MRI FINDINGS

		Presenile onset AD group (n = 13)	*Control group Norm 1 (n = 14)*	*P*	*Senile onset AD group (n = 16)*	*Control group Norm 2 (n = 10)*	*P*
Periventricular hyperintensities							
Caps:	Occipital	1 (0–1)	1 (0–2)	0.38	1.5 (1–2)	1 (0–2)	0.02
	Frontal	1 (1–2)	1 (1–2)	0.59	2 (1–2)	2 (1–2)	0.24
Bands:	Lateral	1 (0–1)	1 (0–1)	0.59	2 (1–2)	1 (1–2)	0.004
	(Sum score)	3 (1–4)	3 (1–5)	0.31	5 (3–6)	3.5 (3–5)	0.003
White matter hyperintensities							
	Frontal	2 (0–4)	1 (0–2)	0.17	4.5 (1–6)	2 (1–5)	0.004
	Parietal	1 (0–5)	1 (0–2)	0.48	2 (0–6)	1 (0–3)	0.02
	Occipital	0 (0–6)	0 (0–1)	0.47	1 (0–6)	0 (0–3)	0.11
	Temporal	0 (0–1)	0 (0–1)	0.56	0 (0–5)	0.5 (0–2)	0.81
	(Sum score)	4 (0–9)	2 (0–5)	0.09	8.5 (4–21)	3.5 (1–10)	0.003
Basal ganglia hyperintensities							
	(Sum score)	0 (0–3)	0.5 (0–2)	0.41	2 (0–6)	0 (0–3)	0.004
Infra-tentorial foci of hyperintensity							
	(Sum score)	0 (0–3)	0 (0–3)	0.33	0.5 (0–8)	0 (0–6)	0.22

Median (minimum-maximum) of white matter scores in disease groups and controls. *P*-values for differences are given (Mann-Whitney U test).

to the lateral ventricles and the PVH (sum) score were found between senile onset AD patients and the Norm 2 group. We detected significant differences between senile onset AD patients and the Norm 2 group in frontal and parietal lobar white matter scores, and in the total WMH score. The BGH score differed significantly from controls, while the ITFH score did not.

In Fig. 2A,B,C the actual number of patients in each group displaying a certain sum score of WMH, PVH and BGH is given, together with the median score of each group. In Table 4 the frequency of lobar white matter scores higher than 1 in each region for the four groups is shown. The highest frequency is found in senile onset AD patients in the frontal and parietal white matter.

The results of the multiple regression analysis are summarized in Table 5. As can be seen in Table 5A, PVH scores depended significantly on age ($P = 0.028$). Corrected for age the PVH scores for presenile onset AD did not differ significantly from controls, whereas the age-corrected average PVH score for senile onset AD patients differed significantly from controls ($P = 0.0002$). From the regression coefficients and the covariance matrix of the estimates (not shown) the age corrected difference in PVH scores between presenile onset AD and senile onset AD can be calculated. We found that PVH scores were higher in senile onset AD patients than in presenile onset AD patients ($P = 0.002$).

As can be seen in Fig. 2B, WMH scores show more variance (scatter) among senile onset AD patients than among presenile onset AD patients and controls. To allow for this inequality in variance a weighted multiple regression was performed (Snedecor and Cochran, 1980). The results of this weighted regression are shown in Table 5B. The

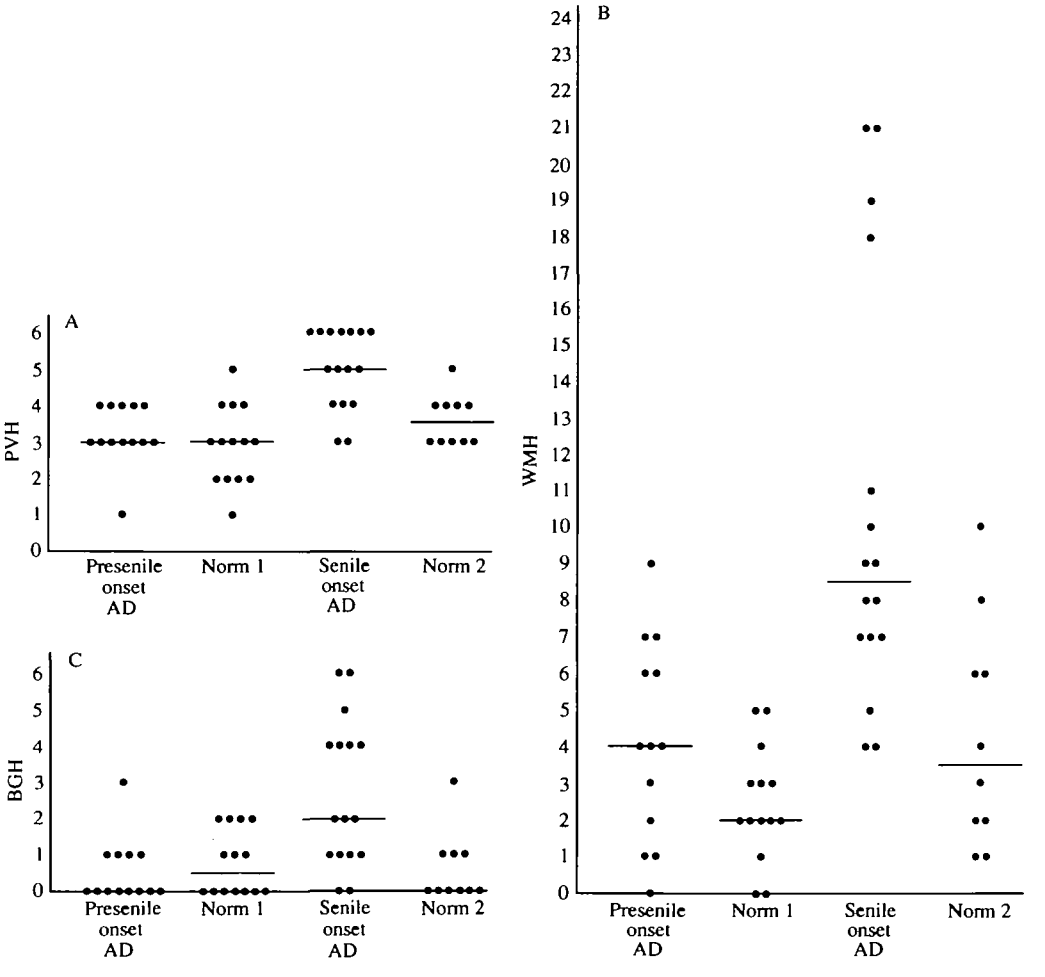

FIG. 2. Scatter graphs showing the number of subjects in the four groups and their respective PVH total scores (A), WMH sum of scores (B, and BGH sum of scores (C). The horizontal lines represent the median scores. (The median scores for BGH in presenile onset AD and Norm 2 were zero.)

results for WMH are the same as those for PVH, except that there is no significant age dependency ($P = 0.24$). The age-corrected difference in WMH scores between senile onset AD and presenile onset AD was significant ($P = 0.006$).

The results for the BGH scores show great similarity to the WMH results (Table 5c). The age-corrected difference in BGH scores between senile onset AD and presenile onset AD was significant ($P = 0.004$).

The difference in cortical atrophy between the AD patients and controls reached statistical significance in both the temporal and frontal regions. We failed to find a significant difference in cortical atrophy in any of the four regions between presenile onset AD and senile onset AD patients.

TABLE 4. NUMBER OF PATIENTS (PERCENTAGE) DISPLAYING A SCORE WMH HIGHER THAN 1

	Presenile onset AD group (n = 13)	*Control group Norm 1 (n = 14)*	*Senile onset AD group (n = 16)*	*Control group Norm 2 (n = 10)*
White matter hyperintensities				
Frontal	6 (46)	5 (36)	14 (88)	4 (40)
Parietal	4 (31)	3 (21)	12 (75)	3 (30)
Occipital	2 (15)	0 (0)	6 (37)	1 (10)
Temporal	0 (0)	0 (0)	3 (19)	1 (10)

TABLE 5.

Variable	*Coefficient*	*SD*	*P*
A. Results of regression analysis on PVH			
Age	0.05	0.02	0.028
Presenile onset AD	0.32	0.35	0.37
Senile onset AD	1.42	0.35	0.0002
B. Results of weighted regression analysis on WMH			
Age	0.08	0.06	0.24
Presenile onset AD	1.39	0.96	0.16
Senile onset AD	6.74	1.63	0.0001
C. Results of regression analysis on BGH			
Age	0.01	0.03	0.66
Presenile onset AD	−0.09	0.50	0.86
Senile onset AD	1.88	0.49	0.0001

DISCUSSION

Using semiquantitative assessment of signal hyperintensities we found higher white matter scores and basal ganglia scores in senile-onset AD than in presenile AD and age-matched controls. Grey matter involvement (cortical atrophy) proved to be equal in both demented groups.

We used a scoring system in which periventricular and subcortical white matter hyperintensities as well as the hyperintensities in the region of the basal ganglia and infratentorial region were rated separately. Risk factor analyses and results of functional studies have suggested different aetiologies for subcortical white matter foci and periventricular 'caps and bands' (Fazekas *et al.*, 1987; Kertesz *et al.*, 1988; Fazekas, 1989; Kobari *et al.*, 1990). Therefore, a distinction in scoring seems appropriate, but is not generally applied (Brant-Zawadzki *et al.*, 1985; Kertesz *et al.*, 1990). Additionally, contrary to a global score provided by the Fazekas score, our method produces regional, surface-based information with optimal use of high sensitivity MRI to detect minimal changes in the white matter. We will discuss our findings further below with respect to the different localizations of the hyperintense foci and with respect to possible heterogeneity of AD.

Periventricular hyperintensities

In agreement with preceding reports (Sze *et al.*, 1986; Zimmerman *et al.*, 1986; Drayer, 1988; Fazekas, 1989; Hendrie *et al.*, 1989) we found a significant dependency

on age for PVH. Sze *et al.* (1986) have shown that high signal intensity around the frontal horns (caps) may be explained by (an age-related) loss of ependyma in the frontal horns, with subsequent increased water content in the local brain parenchyma. Similar findings were reported recently by Leifer *et al.* (1990). Our results, however, are contrary to those of McDonald *et al.* (1991) and Fazekas *et al.* (1987) who reported higher PVH scores (rated with the Fazekas' system) in a presenile AD group, compared with age matched controls. The latter authors, however, could themselves not replicate these findings in another study (Fazekas *et al.*, 1991). Both ours and Fazekas' scoring method suffer from overlap between PVH and WMH scores, when large caps are present. Arbitrarily, we rated large caps exceeding 10 mm as WMH, in our study, to avoid rating them twice, both as PVH and WMH (*see* Fig. 1). Yet, the difference between presenile onset AD and senile onset AD patients in the occipital caps and PVH scores we found, may still partly result from an overlap with WMH scores in the occipital and parietal white matter.

White matter hyperintensities

Subcortical and deep white matter hyperintensity scores, especially in the frontal and parietal regions, were significantly higher in the senile onset AD group than in the age-matched control group. An explanation for this regional predominance might be that these areas are overrepresented on axial slices, compared with the relatively small occipital area. Rating signal intensities in the temporal region was troubled by flow artefacts. Since no flow compensating gradients were used, possible differences between groups were less detectable.

By means of multiple regression analysis we were able to show a significant dependency of the sum score WMH on the diagnosis of senile onset AD versus presenile onset AD, unrelated to the differences in age. This means that WMH scores in senile onset AD patients were higher than could be expected for their age.

There may be several explanations for this. First, although we rigorously excluded vascular risk factors in all subjects and all patients had Hachinski scores ranging from 0 to 4, the senile onset AD patients may contain some patients with mixed dementia. It has been argued earlier that demented patients who exhibit low Hachinski scores may represent AD patients, or may be suffering from Binswanger's disease or in fact all other vascular dementias without clinically evident strokes (O'Brien, 1988). In the study by Mölsä *et al.* (1985) 50% of the pathologically proven mixed cases had Hachinski scores lower than 5. Results from functional studies have indicated that the presence of leuko-araiosis is associated with decreased cerebral blood flow in patients with multi-infarct dementia as well as in senile onset AD patients (De Reuck *et al.*, 1991). Secondly, WMH probably result from a subacute hypoperfusion/hypoxic process (Ferrer *et al.*, 1990), and higher scores may reflect the presence of more severe cerebral amyloid angiopathy (Gray *et al.*, 1985; Scheinberg, 1988; Janota *et al.*, 1989; Haan *et al.*, 1990) or some form of neurogenic vasculopathy induced by AD, as suggested by Scheibel *et al.* (1987). On the other hand, cerebral amyloid angiopathy is not reported to differ considerably between early and late onset AD (Vinters, 1987), and severe cerebral amyloid angiopathy often produces brain haemorrhage (Vinters, 1987; Haan *et al.*, 1990), which was not present in any of our patients. We were able to obtain pathological confirmation of the diganosis AD in four senile onset AD patients. In all, the (frontal)

white matter showed arteriolosclerosis with severe loss of axons and demyelination, in the absence of hypertensive changes and amyloid angiopathy, in agreement with earlier findings (Brun and Englund, 1986; Van Swieten *et al.*, 1991). Thirdly, Wallerian degeneration has been put forward as the origin of WMH by Leys *et al.* (1991) and Leifer *et al.* (1990). If this were the case, one would expect more involvement of the subcortical U-fibres. In addition, cortical atrophy was the same for presenile onset AD and senile onset AD, suggesting equal grey matter involvement, which also makes Wallerian degeneration less likely as the causative factor for WMH.

Basal ganglia hyperintensities

Another interesting finding of our study comprises the significantly higher BGH scores in senile onset AD patients, unrelated to age differences. In view of our definition of signal hyperintensities, identified at TE 60, these represent real hyperintensities and not lacunes or Virchow Robin spaces. Similar lesions may be seen on MRI scans of patients with Binswanger's disease but the absence of cortical lesions virtually rules out this diagnosis (Révész *et al.*, 1989). However, hyperintensities in these regions have been mentioned as an argument in favour of coexistence of vascular and Alzheimer's dementia (Tatemichi, 1990). They may have been missed in earlier studies since other rating scales do not identify such lesions.

Infratentorial foci of hyperintensity

No differences were found in the hyperintensity scores of the infratentorial region between the four groups. This may be due to the fact that grading signal hyperintensities in this region is troublesome. Moreover, this region is commonly not affected in AD.

Heterogeneity of Alzheimer's disease

Our findings again raise the question as to whether AD constitutes one or several diseases (Gottfries, 1989*a*). Despite variations in clinical presentation (disturbed language functions, extrapyramidal signs, mood disturbances), AD is still considered to be one single disorder because of the neuropathological similarities (neurofibrillary tangles and senile plaques in the neocortex) in all types. However, clinical and psychiatric observations (Burns *et al.*, 1990; Blennow *et al.*, 1991) as well as neurochemical studies (Rossor *et al.*, 1984; Gottfries *et al.*, 1985; Svennerholm *et al.*, 1987) have provided evidence that AD consists of at least two disorders, with different ages at onset. We have not investigated whether differences in white matter involvement would contribute to clinical differences between subtypes of AD, as suggested by Englund *et al.* (1989) and Kertesz *et al.* (1990), since we matched our dementia groups on the basis of clinical disease severity, thus creating groups only differing in the age at onset of disease.

In reports in which CT and MRI have been used to detect white matter changes in AD, a distinction between presenile onset AD and senile onset AD has generally not been made. This may explain why some authors report small differences in white matter changes between AD patients and normal elderly (Rezek *et al.*, 1987) and others do not (Kozachuk *et al.*, 1990; Leys *et al.*, 1990). For example, in the study of Leys *et al.* (1990) in which 17 AD patients were included, of whom 14 had presenile onset, no differences in white matter changes between AD patients and normal controls were shown. Their results are in agreement with our study, but their conclusion is only applicable

to the presenile form. Wallin *et al.* (1989) and Blennow *et al.* (1991) demonstrated a difference between early and late onset AD with respect to white matter involvement, using CT. Given the fact that leuko-araiosis on CT correlates well with WMH on MRI (Hachinski *et al.*, 1987; Leys *et al.*, 1990), our results are comparable with theirs. However, they did not include age-matched controls, hence their findings may be secondary to age differences alone.

Our scoring system shows that grading white matter lesions is not straightforward, which makes comparison with other studies difficult. If we arbitrarily decide that a score higher than 1 (*see* Table 2) may be considered 'severe', then a majority of senile onset AD patients (88%) shows severe frontal white matter involvement, in contrast to a minority of the presenile onset AD (46%) patients (Table 4). If the origin of these abnormalities is indeed 'a small vessel disease', e.g. arteriolosclerosis with chronic ischaemia (van Swieten *et al.*, 1991), in order to select a homogeneous group of AD cases for research purposes and evaluations of therapeutic strategies, MRI should be added to exclude patients displaying severe white matter changes. However, no studies investigating the origin of white matter hyperintensities specifically in AD patients have been reported yet, and normative data for white matter hyperintensities in healthy elderly subjects without cerebrovascular risk factors should be provided first.

Our data confirm that one has to be cautious in diagnosing patients with white matter lesions, as 'senile dementia of Binswanger's type' as suggested by Román (1987). These lesions may be present in patients fulfilling research criteria for probable AD, and even in healthy elderly persons without any of the clinical features ascribed to Binswanger's disease (Bennett *et al.*, 1990).

In conclusion, our findings lend support to the growing belief that clinically diagnosed AD is heterogeneous, probably consisting of 'pure' and 'mixed' cases, the latter usually with later disease onset and displaying more white matter signal hyperintensities on MRI than normal for age, suggesting other (microvascular) contributing pathogenetic factors.

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