A White Matter Disorder in Dementia of the Alzheimer Type: A Pathoanatomical Study

A. Brun, MD, and E. Englund, MD

In cases of Alzheimer's presenile and senile dementia, Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT), respectively, we have observed, in addition to the gray matter degeneration, a lesion that has the character of an incomplete infarction confined to the white matter. It is encountered in 60% of both groups, with mild changes in two thirds and moderate or severe changes in one third. It involves the deep white matter symmetrically, tapering off toward the cortex. It is characterized by partial loss of myelin, axons, and oligodendroglial cells; mild reactive astrocytic gliosis; and sparsely distributed macrophages as well as stenosis resulting from hyaline fibrosis of arterioles and smaller vessels. No complete or cavitating infarctions and no hypertensive vascular changes were observed. The white matter changes are thought to be due to hypoperfusion of the concerned white matter territories since, in addition to the white matter hyaline vascular stenosis, these cases show signs of cardiovascular disease, usually with hypotension.

The white matter disorder also occurs independent of the gray matter process of AD and SDAT and may be seen as the sole brain lesion in non-AD subjects. Its occurrence is thus neither regularly related to the severity nor to the regional appearance and accentuation of the cortical Alzheimer process and is thus not likely to be just the result of a wallerian degeneration. Histologically it is similar in several respects to Binswanger's disease, although with some distinct differences. It is thus related to the cerebrovascular group of disorders in addition to AD and SDAT. In view of its frequency and severity, this white matter lesion is important to define, to diagnose, and ultimately to prevent or cure.

Brun A, Englund E: A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 19:253–262, 1986

The Alzheimer type of presenile (AD) and senile dementia (SDAT) is the major cause of organic dementia. Symptoms are thought to be due to a gray matter disorder. This may, however, not be the sole explanation. In our studies of these diseases we have frequently observed a concurrent white matter disorder that has hitherto been largely neglected in histopathological studies. The aim of the present report is to describe this white matter disorder, to distinguish it from other white matter changes, and to consider possible pathogenetic mechanisms and diagnostic problems.

Materials

A total of 84 patients were studied. Among these, 20 had AD and 28 had SDAT (Tables 1, 2). For comparison we included in the material 23 patients with multi-infarct dementia (MID). Also studied was 1 patient with senile dementia, clinically diagnosed as having "progressive vascular dementia," though histopathologically the disorder was neither of the ordinary MID nor SDAT type. This patient is referred to as Patient X (Table 3). This patient had no gray matter degeneration and was included for the possible bearing of the case on pathogenetic considerations.

The material represents consecutive cases of dementia of the types under consideration, studied at our department during a period of 5 years. Excluded were patients with inadequate histological work-up. All patients with dementia were diagnosed clinically. With the exception of 12 patients, all cases were monitored with regional cerebral blood flow (rCBF) measurement, psychometric testing, and psychiatric evaluation, following a routine program at the University Hospital. The results of these investigations, in part previously presented [6, 15], correlated well with the histopathological findings and are not presented in detail here. Twenty-six nondemented normotensive control subjects were included, age range 49 to 69 years (10 patients) and 70 to 100 years (16 patients) (Tables 1, 2).

Methods

At postmortem examination, the brains of the demented patients were weighed, fixed in formalin, and cut in 1-cm-thick whole-brain coronal slices. Roughly every other slice

From the Institute of Pathology, Department of Neuropathology, University Hospital, S-221 85 Lund, Sweden.

Received Oct 29, 1984, and in revised form Mar 18, 1985. Accepted for publication Aug 10, 1985.

Address reprint requests to Dr Brun.

Table 1. Data on Patients with Alzheimer's Disease Ranked According to Severity of Alzheimer Encephalopathy and on 10 Age-Matched Control Subjects

AE Ranking	Age (yr)	Dementia (yr)	Cardiovascular Disorder[a]	Heart Weight (gm)	Brain Weight (gm)	White Matter Lesions[b]
Mild	66	4	+ −	420	1,240	I
	66	6	0	?	1,360	I
	69	10	0−	250	1,210	...
	60	10	0	230	1,210	...
Mild to moderate	66	3	+	430	1,400	...
	69	9	0	?	1,130	...
	79	17	+	370	1,180	...
Moderate	66	5	0	300	1,170	II
	55	6	0−	?	910	...
	71	7	0	190	1,100	...
	65	7	+	350	1,300	II
	70	13	0	?	860	...
	52	16	0	230	930	I
Moderate to severe	69	7	0	350	1,060	III
Severe	66	3	0−	340	1,340	I
	62	10	0−	?	850	I
	70	11	0	?	910	...
	74	11	0−	170	740	III
	61	16	0	210	880	I
	73	17	+ −	500	1,120	I
Mean of patients	66					
Control	49	...	0	280	1,440	...
	54	...	0	410	1,250	...
	56	...	0	?	1,360	...
	58	...	0	250	1,440	...
	60	...	?	?	1,510	...
	61	...	0	?	1,530	...
	65	...	+	330	1,340	...
	67	...	0	250	1,390	...
	67	...	+ +	520	1,340	...
	69	...	+	500	1,390	...
Mean of controls	61					

[a]0 = no cardiovascular disorder; + = cardiovascular disorder without blood pressure abnormalities recorded; + + = cardiovascular disorder with longstanding hypertension recorded; + − = cardiovascular disorder with longstanding or episodic hypotension recorded; − = longstanding or episodic hypotension recorded.
[b]I = mild; II = moderate; III = severe.

AE = Alzheimer's encephalopathy.

was embedded, sectioned, and stained according to routine procedures, including myelin staining with Luxol fast blue (LFB). Control specimens were treated in the same way but with fewer sections. The sections were then studied for type of changes as well as regional distribution of changes in gray and white matter. With regard to the cortical changes, the 48 patients with SDAT and AD were ranked according to the degree of severity (Tables 1, 2), using a grading system of 0 to IV as described in a previous publication [5]. It is sufficient to mention that Grade 0 is a basic stage of pronounced aging or incipient AD and the following grades represent increasingly severe stages.

White matter lesions were ranked as mild, moderate, or severe, with respect to the severity as well as to the extent of degeneration (in Tables 1 and 2 referred to as *I, II,* and *III*). Patients with minimal or questionable white matter changes were ranked as normal. The case histories as well as data from autopsy reports of all cases were searched for information on cardiac and cardiovascular disorders and for general features. This included a history of symptomatic ischemic heart disease with myocardial infarction, chronic or recurrent arrhythmia, and confirming electrocardiographic tracings. Increased heart weight, shown to correlate significantly with hypertension [30], was noted. Noted also were abnormalities in blood pressure, recorded as more than occasional, and autopsy findings of myocardial infarction, cardiosclerosis, or hypertensive angiopathy of various organs including the brain. Recording of blood pressure was at times incomplete, but sufficient documentation was obtained in half of the patients.

Results

Cardiovascular Disorder—Clinical and General Pathological Findings

In the 20 patients with AD, 5 had evidence of a cardiovascular disorder. Among these 5, no arrhythmias

Table 2. Data on 28 Patients with Senile Dementia of the Alzheimer Type Ranked According to Severity of Alzheimer's Encephalopathy and on 16 Age-Matched Controls

AE Ranking	Age (yr)	Dementia (yr)	Cardiovascular Disorder[a]	Heart Weight (gm)	Brain Weight (gm)	White Matter Lesions[b]
Mild	87	0.5	+ −	410	1,160	II
	87	1	+	430	1,270	I
	81	2	0 −	370	1,210	...
	71	3	0	270	1,360	I
	83	3	+ −	280	1,040	...
	84	4	+ −	380	1,400	...
	79	5	+ −	330	1,100	...
	85	5	+ −	250	1,230	I
	83	?	+ −	380	1,260	I
Mild to moderate	89	1	+ −	360	1,010	I
	67	2	0	280	1,200	...
	80	4	0	450	1,200	...
	77	6	0	220	1,150	I
	92	6	+ −	330	1,110	I
Moderate	89	2	+	450	?	I
	70	3	+	400	1,290	I
	80	3.5	+	400	1,180	II
	84	5	+ −	280	1,180	II
	85	6	+	260	980	I
	80	7	+ −	320	1,170	...
Moderate to severe	78	6	+	280	1,050	III
	77	8	+	470	980	I
	84	10	+	240	950	III
Severe	72	3	+	410	1,200	...
	79	4	0	370	1,260	I
	81	6	0	260	980	...
	71	10	+	260	920	III
	92	13	+ −	?	1,060	I
Mean of patients	81					
Control	70	...	+	540	1,240	...
	71	...	+	420	1,405	...
	72	...	+	570	1,410	...
	73	...	0	350	1,095	...
	75	...	0	?	1,140	...
	76	...	+ +	390	1,200	...
	77	...	+	450	1,260	...
	80	...	0	250	1,100	...
	80	...	+	440	1,350	...
	82	...	0	320	1,100	...
	84	...	0	310	1,220	...
	85	...	+	680	1,310	...
	90	...	+	390	1,120	...
	90	...	+	400	1,120	...
	100	...	0	320	?	...
	100	...	0	270	980	...
Mean of controls	82					

[a]0 = no cardiovascular disorder; + = cardiovascular disorder without blood pressure abnormalities recorded; + + = cardiovascular disorder with longstanding hypertension recorded; + − = cardiovascular disorder with longstanding or episodic hypotension recorded; − = longstanding or episodic hypotension recorded.
[b]I = mild; II = moderate; III = severe.

AE = Alzheimer encephalopathy.

were observed. One of 20 was hypertensive late in life (blood pressure, 210 to 225/110 mm Hg), and 1 had had hypotension for several years (blood pressure, 90 to 110/55 to 70). Blood pressure in the other 18 patients ranged from 130 to 180/80 to 90, although in several patients a low blood pressure of 105/65 was occasionally recorded. There was no nephrosclerosis and there were no embolic infarctions in the kidneys or the spleen.

In the SDAT group, 21 of the 28 patients had evidence of a cardiovascular disorder and arrhythmia was documented in 7 of these. None of the 28 patients was hypertensive, 6 were consistently hypotensive (blood pressure, 90 to 120/50 to 65), and most of the other 22 patients had episodes of hypotension, between which blood pressure was normal, i.e., 130 to 180/70 to 95—generous limits for the aged. There was no nephrosclerosis. Embolic infarctions in the kidneys and the spleen occurred in 2 patients with known mild hypertension.

Twenty-two of the 23 patients with MID had evidence of a cardiovascular disorder; in 10 of these, a cardiac arrhythmia was part of the disorder. Most patients were diagnosed as hypertensive (recorded blood pressure, 190 to 210/100 to 115), but several had occasional recordings of low blood pressure later in life. Nephrosclerosis and embolic infarctions in the kidneys and/or spleen were regular findings.

Patient X had a history of hypertension (blood pressure, 180 to 220/100) for 2 years or more. Four years before death, blood pressure decreased to 110 to 120/85 to 90 and during these years symptoms of dementia developed. Cause of death was a myocardial infarction, atrial fibrillation, and cardiac failure. Postmortem examination revealed severe general arteriosclerosis. There were no embolic infarctions.

Twelve of the 26 controls had cardiovascular disease; 2 were hypertensive. Benign nephrosclerosis occurred in a few subjects, but there were no embolic infarctions.

Diabetes mellitus, thyroid disorders, and pulmonary disease occurred sporadically in all groups, but not as a consistent feature.

Pathoanatomical Gray Matter Findings in SDAT and AD

All patients with SDAT or AD showed an Alzheimer's encephalopathy above Grade 0. The degenerative changes constituting the encephalopathy consisted of senile plaques, neurofibrillary tangles, reactive gliosis, spongiosis, congophilic angiopathy, degeneration, and loss of nerve cells. This was accompanied by blurring of the cortical lamination and shrinkage of the cortex.

The regional distribution of these changes was consistent and best seen in the moderately and severely affected patients (Fig 1); this agreed with earlier presentations [5, 11, 15]. Alzheimer's encephalopathy most severely involved the basal and medial temporal lobe, including the amygdala, hippocampus, uncus, and entorhinal cortex, followed by the parietal lobe and the posterior part of the cingulate gyrus. The frontal lobe was less severely involved, while the sensorimotor and occipital lobe, particularly the calcarine area and the anterior cingulate gyrus, were relatively spared, except when the disease was very advanced.

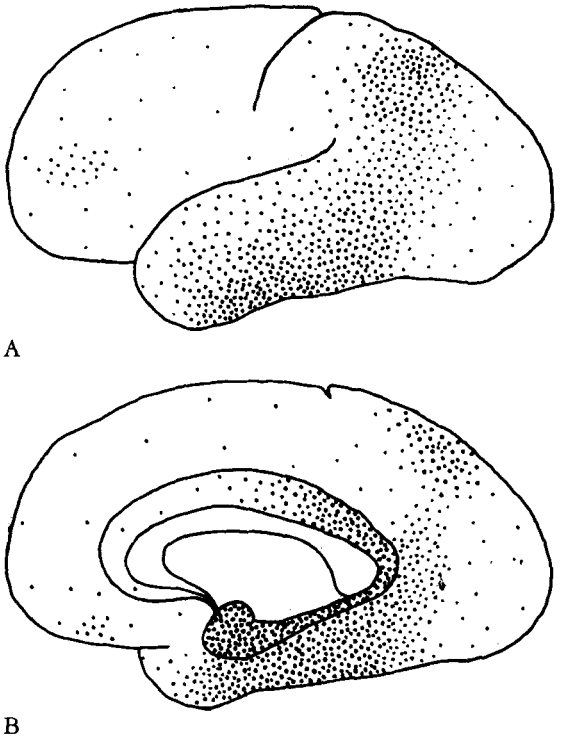

Fig 1. Distribution of gray matter changes in senile dementia of the Alzheimer type and Alzheimer's disease (typical case), with shading intensity paralleling severity. (A) Lateral and (B) medial views.

The basal ganglia showed occasional lacunar infarctions. In the thalamus and corpus striatum, there was no atrophy, senile plaques, neurofibrillary tangles, or other degenerative changes seen on light microscopy.

In the patients with SDAT or AD, intracranial amyloidosis was present in the senile plaques and in many vessels. Congophilic angiopathy was seen in the cortex and meninges in 14 patients with AD and 19 patients with SDAT, but not in the white matter. Cerebral hypertensive angiopathy, i.e., with spiraling of the vessels, microaneurysms, necroses, or hemorrhages of the vessel walls, was observed in 2 patients with AD and 4 with SDAT. In these 6 patients the angiopathy was moderate and confined to the larger cortical and meningeal arteries.

Pathoanatomical White Matter Findings in SDAT and AD

In addition to the changes in the gray matter described, 30 of 48 patients with SDAT or AD showed

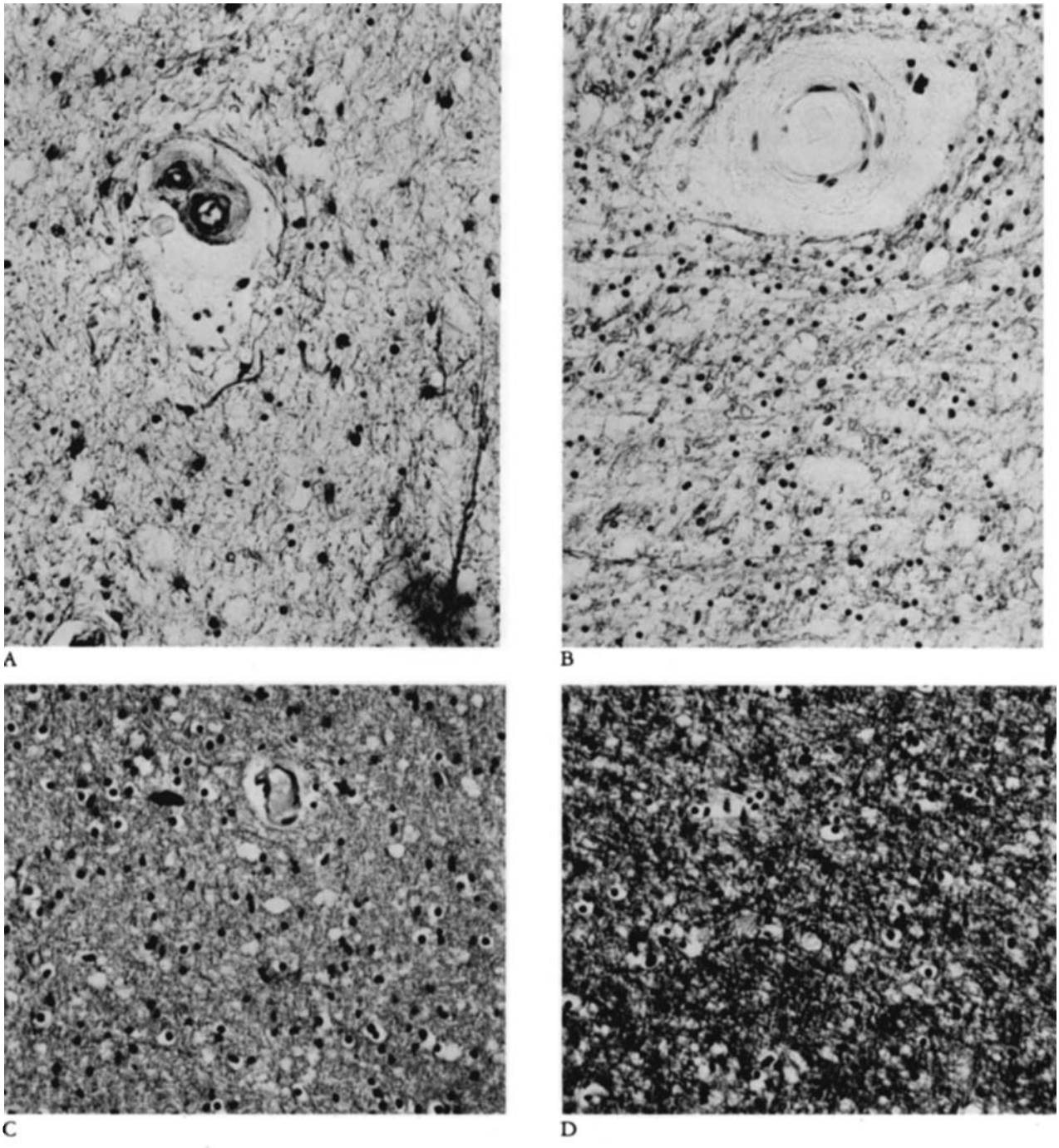

Fig 2. Frontal white matter in a patient with senile dementia of the Alzheimer type with (A, B) mild to moderate changes compared with (C, D) normal white matter. Note the attenuation of tissue with partial loss of oligodendroglial cells (A, B) and myelin sheaths (B), reactive astrogliosis (A), and a fibrohyaline arteriosclerosis (A, B). ({A, C} H&E, {B, D} Luxol fast blue; ×250.)

widening of the ventricular system and changes in the white matter (Tables 1, 2). These abnormalities were not readily apparent at gross sectioning, but appeared macroscopically as pale areas on the sections stained for myelin. None of the brains had an abnormally high weight or signs of edema.

Microscopically, the picture of white matter changes was that of partial loss of axons, myelin sheaths, and oligodendroglial cells, which resulted in tissue attenuation; slight reactive astrocytosis; and the presence of a few macrophages (Fig 2A, B). Varying numbers of intact axons with myelin sheaths ran through these

areas and no complete infarctions and no cavitations were observed. The spared myelin sheaths and oligodendroglial cells were not swollen. Many of the smallest arterioles and capillaries showed a fibrohyaline thickening of the wall, almost obliterating some vessels, whereas others in the same region were apparently spared. These vessels did not stain with Congo red.

The fibrohyaline arteriolosclerosis of the white matter did not correlate with the presence of congophilic angiopathy in the cortex, and no cortical arterioles showed fibrohyaline sclerosis. No emboli or thrombus remnants were seen in the cerebral vessels, and no hypertensive angiopathy was identified.

White matter lesions were ranked in three steps from normal to completely destroyed tissue. Absence of any changes (normal tissue) is illustrated in Fig 2C and D. The three degrees of white matter lesions consisted of loss of oligodendroglial cells and axons, reactive astrocytosis, and arteriolar changes, all gradually increasing in extent and severity, but not as far as complete destruction (Fig 3). Mild changes occurred in 20 patients; in 10 the lesions were moderate or severe (Tables 1, 2).

Topographic distribution of white matter changes was studied as well. The white matter was affected in a predominantly symmetrical fashion, the attenuation extending from a periventricular location in all directions toward the periphery to a degree that varied from patient to patient (Fig 4). In the most severe cases the changes engaged the whole white matter, sparing only the subcortical U fibers (Fig 5). Lesions were most easily observed in the frontal lobes, central regions, and parietal lobes.

A severe white matter disorder occurred somewhat more frequently with severe than with mild cortical Alzheimer's encephalopathy in both SDAT and AD (Tables 1, 2). However, in the patients with SDAT or AD with mild cortical changes, the white matter was variable, and ranged from normal to severely altered in appearance. Regions with pronounced white matter changes were often adjacent to a spared cortical strip, but degenerated cortex could also border normal white matter; thus, there was no apparent local correlation between Alzheimer's encephalopathy and white matter lesions. The only consistent exception to this was a slight loss of myelin noted in the temporal lobes of several patients with SDAT or AD. The myelin loss here was subjacent to temporal cortical areas with considerable cortical involvement.

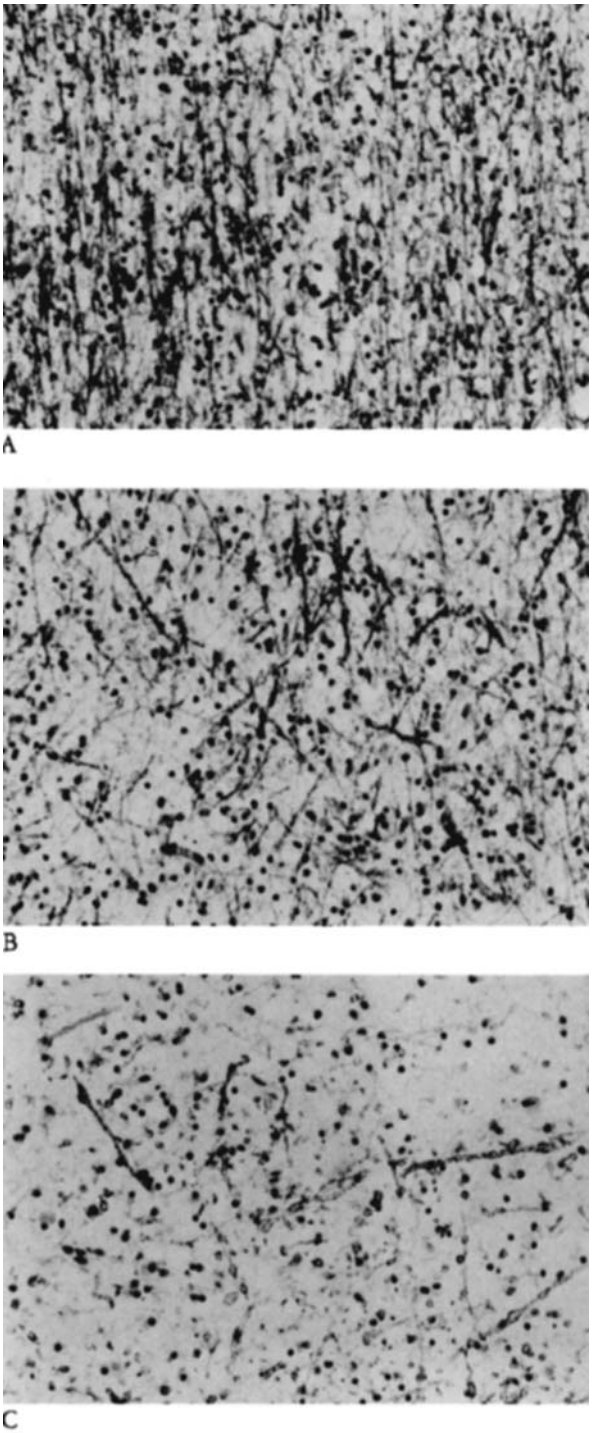

Fig 3. Central white matter in a patient with senile dementia of the Alzheimer type who had lesions varying from mild (A) to moderate (B) to severe (C). (Luxol fast blue; ×250 before 24% reduction.)

Pathoanatomical Gray and White Matter Findings in MID

Most patients with MID had scattered and asymmetrically distributed complete infarctions of the gray matter, with or without cavitation. The basal ganglia generally showed small lacunar infarcts. Of the 23 patients with MID, 17 also had a minor (Grade 0) component of Alzheimer's encephalopathy. Most of the patients with MID showed cerebral hypertensive angiopathy, with spiraling of arteries and thickening of arterial walls in both the meninges and the cerebral tissue.

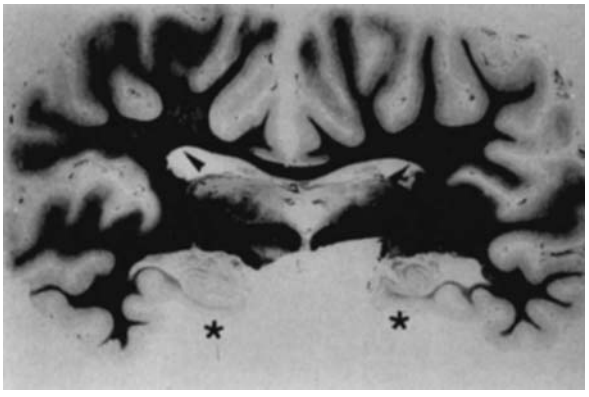

Fig 4. Patient with senile dementia of the Alzheimer type who had white matter changes in the centrum semiovale (arrowheads). *The adjacent cortex has no or slight Alzheimer degeneration (i.e., encephalopathy {AE}). There are no complete infarctions in gray or white matter. Compare with slight paling of the temporal white matter, here adjacent to a region with severe AE and temporal cortical atrophy; note pronounced atrophy of the hippocampus (*). (Luxol fast blue.)*

The white matter had multiple asymmetrically distributed, complete infarctions surrounded by a transitional zone of reactive gliosis and loss of tissue components, normalizing toward the unaffected periphery. In 4 of these patients, the areas of complete infarction were small, while incomplete destruction was extensive, spreading into most parts of the white matter. Thus, in these patients, the damage was predominantly subcortical, with only minor cortical involvement (Table 3).

Pathoanatomical Findings in Patient X

In Patient X there was an incomplete infarction-like disorder that was exclusively confined to the white matter. It was mild to moderate and histologically of the same type as that in the patients with SDAT or AD. It was located in the frontal lobes, extending toward the parietooccipital and temporal regions with decreasing severity. In addition to a stenosing, fibrohyaline sclerosis of many of the white matter arterioles and capillaries, there was widespread cerebral arteriosclerosis with narrowing of several arachnoid vessels. The cortex showed occasional neurofibrillary tangles and a few senile plaques, but there was no clear-cut Alzheimer encephalopathy and no infarction.

Findings in the Control Group

No changes were found in the gray matter of the control subjects. The oldest 4 had slight loss of myelin and widening of the ventricles, and in 9 periventricular hyaline arteriolosclerosis was seen, but without white matter changes. These vessel wall changes affected

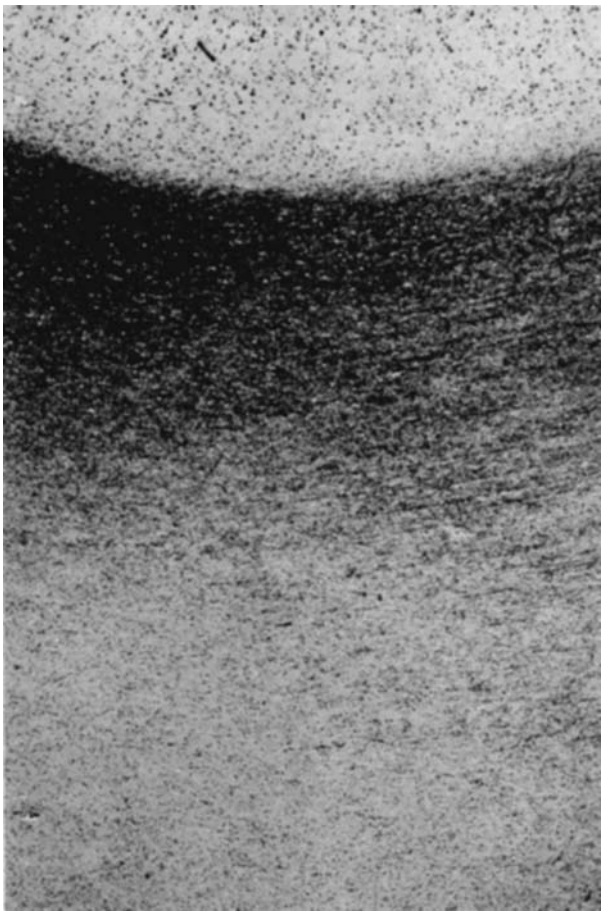

Fig 5. Patient with Alzheimer's disease who had white matter changes in the centrum semiovale, corresponding to low staining intensity. The subcortical U fibers are spared. Microscopically the adjacent cortex was relatively spared with respect to Alzheimer's encephalopathy. (Luxol fast blue; ×25.)

only a few vessels in a limited area around the ventricles. Two control subjects had slightly more pronounced white matter changes that were mild but histologically similar to those of the patients with AD/SDAT. These changes were located in the frontal and parietal lobes. There was no hypertensive angiopathy seen in the controls.

Artifacts

The white matter lesions in the patients with SDAT or AD appeared macroscopically as pale areas in the myelin-stained slides. Pale areas were also seen in some SDAT and AD cases without white matter lesions and in some normal subjects, but microscopy revealed normal conditions: intact axons and a normal number of oligodendroglial cells, no fibrohyaline arteriosclerosis, and, most important, no cell reaction. The artifactual nature of these findings was also confirmed by the absence of tissue attenuation by other stains.

Table 3. Data on 23 Patients with Multi-Infarct Dementia Ranked According to Duration of Dementia and Patient X[a]

Age (yr)	Dementia (yr)	Cardiovascular Disorder[b]	Heart Weight (gm)	Brain Weight (gm)
81	0.5	+	440	1,010
79	0.5	+ −	390	1,250
88	1	+ −	320	900
63	1	+ +	380	1,220
76	1	+ −	350	1,160
58	1.5	+ −	300	1,200
88	1.5	+ −	520	1,500
81	1.5	+ −	330	1,280
82	2	+	400	1,050
79	2	+	420	980
68	3	+ +	360	1,680
83	3	+ −	310	1,420
87	3	+	420	1,330
83	3	+ +	460	1,100
84	3	+ +	560	1,250
96	3	+ −	380	1,220
83	3	+ −	350	1,110
83	3	+ +	430	1,150
72	3	+ −	...	1,420
74	?	?	...	...
88	5	+ −	480	980
82	5	+ −	250	1,160
83	7	+ +	450	1,250
91 (Patient X[a])	4	+ −	390	1,100

[a]See text for description.
[b]+ = cardiovascular disorder without blood pressure abnormalities recorded; + + = cardiovascular disorder with long-standing hypertension recorded; + − = cardiovascular disorder with long-standing or episodic hypotension recorded.

Discussion

The finding of a white matter disorder in many cases of Alzheimer-type dementia [11] initiated this study of consecutive cases of dementia. In addition to the cortical degeneration, a white matter disorder was found in 55% of patients with AD and in 68% of patients with SDAT (Tables 1, 2). Changes were found also in a few controls (2 of 26), within limited areas and to a mild degree; thus, the difference between normal and demented subjects was obvious neuropathologically. A requirement for this study was the use of whole brain sections, without which the changes would have been difficult to detect and map.

Characterization of the White Matter Lesions

Macroscopically changes usually escaped attention but were seen as pale areas without specific features on myelin-stained sections.

Microscopically there was partial loss of myelin sheaths, axons, and oligodendroglial cells along with a mild glial reaction and a few macrophages. The smallest arterioles and capillaries within the damaged areas showed a stenosing fibrohyaline sclerosis, but without hypertensive alterations. We regard these changes as incomplete infarctions confined to the white matter, for the following reasons. The changes are similar to those of the transitional zone surrounding many complete infarctions, as in patients with MID. A hypothetical increase in the severity of changes would in our opinion result in a complete infarction, a gliotic scar with total loss of functional neuronal tissue, or even cavitation. Microscopically the disorder can also appear as an isolated phenomenon, as shown in our Patient X in whom no other histopathological changes were seen.

Comparison with Other White Matter Disorders

The questions arise: Are the white matter changes primary or secondary to Alzheimer's disease? Could wallerian degeneration due to gray matter disease explain the white matter changes, making them purely secondary to the Alzheimer encephalopathy? Alzheimer degeneration of the gray matter was usually accompanied by mild myelin loss in the temporal white matter, even though the encephalopathy was far more advanced in the hippocampus. This could be an example of wallerian degeneration due to advanced temporal cortical degeneration in AD and SDAT. Also, there is a certain tendency for severe white matter changes to accompany severe AD and SDAT (Tables 1, 2), and this

may be taken as an indication of a pathogenetic relationship between white and gray matter changes. However, gray and white matter changes in most other areas did not concur regionally. Well-preserved gray matter often (e.g., frontally) lay over severely changed white matter, but the reverse involvement was sometimes also found. Furthermore white matter change could occur in the complete absence of gray matter changes as in Patient X. The absence of white matter changes in 45% of patients with AD and 32% of patients with SDAT, irrespective of the severity of Alzheimer's encephalopathy, also makes the possibility of secondary degeneration less likely.

Neuronal loss in the basal ganglia, as well as cortical degeneration, could elicit wallerian degeneration in the white matter. The corpus striatum and thalamus are sites of transmitter changes, but the neuronal drop-out here is mild at worst. The integrity of these structures is attested to by the fact that both the corpus striatum and the thalamus are well preserved metabolically, as shown by positron emission tomographic studies [20]. The involvement, if any, of these structures would likely not produce extensive loss of myelin in the surrounding white matter. Therefore secondary wallerian degeneration does not seem to play an important role in the pathogenesis of the white matter lesions.

In the case of an apallic syndrome, severe cortical neuronal depletion is followed by white matter changes, but here the white matter is already damaged as shown by oligodendroglial loss even in the earliest stages of the brain disease.

Binswanger's disease or progressive subcortical arteriosclerotic encephalopathy is described as a subcortical disease with widespread white matter loss of myelin and scattered complete infarctions in the basal ganglia and the white matter [3, 4, 7, 10, 24, 25, 27, 28, 32, 34]. It is a slowly progressive disease associated with hypertension, and the clinical expression is an Alzheimer-like dementia [14, 19, 21, 26, 29], although patients with heterogeneous clinical pictures have been reported [1]. Chronic edema, as described by Feigin and Popoff [12] and discussed by other authors [17, 33], is morphologically similar to Binswanger's disease in that it is based on hypertension and shares with the latter myelin loss, white matter edema, and gliosis. The white matter disorder in our SDAT and AD material differed from both these conditions in that the white matter disorder was not associated with hypertension. The patients with white matter changes were normotensive and recurrently hypotensive. There were no complete infarctions in the white matter, and small lacunar infarctions in the basal ganglia occurred only occasionally. There also were no hypertensive vascular changes. Microcystic spaces, edematous fluid, and swollen astrocytic processes were lacking and there was no brain weight increase or gross impression of edema. It is nevertheless possible that early edema could have been present as part of an ischemic reaction.

Progressive subcortical gliosis [23] and presenile glial dystrophy [2] are white matter disorders with certain superficial similarities to the changes described here. They are, however, characterized by massive white matter gliosis, with no or only slight myelin loss and no vascular changes. Multiple sclerosis–like lesions have been reported in a number of cases of non-AD dementia [16]. The white matter changes under discussion here are clearly different from those of multiple sclerosis.

The process of aging alone, in a functionally intact brain, can alter the histological and chemical properties of white matter [8, 31]. Briefly, an age-dependent subtle loss of white matter causes widening of the ventricles. In our normal material, a few instances of mild loss of myelin and sclerosis of smaller vessels was found in a narrow, periventricular zone. Two other control subjects had slightly more pronounced myelin depletion. These findings were far less imposing than the white matter changes in the dementia group.

Pathogenetic and Etiological Mechanisms

We can only speculate on the pathogenetic and etiological mechanisms behind the white matter disorder in SDAT and AD. Patients with this disorder had a small-vessel abnormality in deeper regions of the white matter. Patients with Alzheimer's dementia with normal white matter had no or only slight vessel changes, comparable to the aged normal subjects. Cardiovascular disorders with arrhythmia or hypotensive bouts, or both, were a regular finding in patients with the white matter disorder. In these patients hypertension was rare, and evidence for hypotension was by far more common. It is of interest to note that Caplan and Schoene [7], in presenting a pathogenetic hypothesis for Binswanger's disease, noted a thickening and sclerosis of long penetrating white matter vessels and suggested that poor perfusion of the white matter occurred with episodes of hypotension.

It must be emphasized that documentation of blood pressure was sufficient in 50% of our subjects. We speculate that hypotension would have been more prominent in the patient groups, had the recordings been more complete. In addition, we have set the lower limit for normal blood pressure quite low.

Cardiovascular dysfunction resulting in recurrent systemic hypotension and cerebral hypoperfusion in a brain with a vascular abnormality (i.e., small-vessel disease) and locally compromised blood supply may produce the white matter disorder described, namely, a state resembling incomplete infarction. This is illustrated by Patient X, in whom no degenerative gray matter disease existed, but vascular factors of the kind

considered here were present. Similar situations are described by Goto and co-workers [14] and DeReuck and Schaumburg [9].

We do not believe that AD is a major cause of the white matter lesions, but its possible contribution to the pathogenesis cannot be excluded.

White matter changes observed on computerized tomography in patients with dementia [13, 18, 22] may at least in part represent the lesions discussed here and may also be recognizable on magnetic resonance imaging.

It is well known that white matter changes alone can produce dementia, as is the case of Binswanger's disease and progressive subcortical gliosis. Therefore the white matter disorder in SDAT and AD described here probably influences the clinical expression of AD, but how and to what extent are questions still to be answered.

Thanks are due to Kerstin Sturesson and Elsie Andersson for histotechnical assistance, Peter Posselwhite and Roger Lundholm for help with the illustrations, and Gun Kungberg and Elisabeth Borgström for excellent manuscript typing.

References

1. Agnoli A, Ruggieri S, Denaro A, et al: White matter disease (Binswanger's encephalopathy) in chronic cerebrovascular disorders. Monogr Neural Sci 11:144–149, 1984
2. Auff E, Seitelberger F: Contribution to the problem of presenile glial dystrophy. Neuropathology 1:113–118, 1980
3. Biemond A: On Binswanger's subcortical arteriosclerotic encephalopathy and the possibility of its clinical recognition. Psychiatr Neurol Neurochir 73:413–417, 1970
4. Binswanger O: Die Abgrenzung der allgemeinen progressiven Paralyse. Berl Klin Wochenschr 31:1103–1105, 1137–1139, 1180–1186, 1984
5. Brun A, Englund E: The pattern of degeneration in Alzheimer's disease. Neuronal loss and histopathological grading. Histopathology 5:549–564, 1981
6. Brun A, Gustafson L: Distribution of cerebral degeneration in Alzheimer's disease. A clinico-pathological study. Arch Psychiatr Nervenkr 223:15–33, 1976
7. Caplan LR, Schoene WC: Clinical features of subcortical arteriosclerotic encephalopathy (Binswanger's disease). Neurology (NY) 28:1206–1215, 1978
8. Corsellis JAN: Ageing and the dementias. In Blackwood W, Corsellis JAN (eds): Greenfield's Neuropathology. Third edition. London, Arnold, 1976
9. DeReuck J, Schaumburg H: Periventricular atherosclerotic leukoencephalopathy. Neurology (Minneap) 22:1094–1097, 1972
10. Editorial 1981: Binswanger's encephalopathy. Lancet 1:923, 1981
11. Englund E, Brun A: Senile dementia—a structural basis for etiological and therapeutic considerations. In Perris C, Struwe G, Jansson B (eds): Biological Psychiatry 1981. Amsterdam, Elsevier/North-Holland, 1981, pp 951–956
12. Feigin I, Popoff N: Neuropathological changes late in cerebral edema: the relationship to trauma, hypertensive disease and Binswanger's encephalopathy. J Neuropathol Exp Neurol 22:500–511, 1963
13. George AE, deLeon MJ, Ferris SH, Kricheff II: Parenchymal CT correlates of senile dementia (Alzheimer's disease): loss of grey-white matter discriminability. AJNR 2:205–211, 1981
14. Goto K, Ishii N, Fukasawa H: Diffuse white-matter disease in the geriatric population. Radiology 141:687–695, 1981
15. Gustafson L, Brun A, Risberg J: Organic dementia: clinical picture related to regional cerebral blood flow and neuropathological findings. Proceedings of the VII World Congress of Psychiatry 1983, Vienna, New York, Plenum, 1984
16. Heffner RR, Porro RS, Olson ME, Earle KM: A demyelinating disorder associated with cerebrovascular amyloid angiopathy. Arch Neurol 33:501–506, 1976
17. Inzitari D, Bracco L, Capparelli R, et al: Cerebrospinal fluid dynamics, white matter degeneration and mental deterioration in subcortical arteriosclerotic encephalopathy of Binswanger type. Monogr Neural Sci 11:150–156, 1984
18. Jacoby RJ, Levy R: Computed tomography in the elderly. 2. Senile dementia: diagnosis and functional impairment. Br J Psychiatry 136:256–269, 1980
19. Janota I: Binswanger's encephalopathy. Lancet 1:1054, 1981
20. Kuhl DE, Metter EJ, Riege WH: Patterns of cerebral glucose utilization in depression, multiple infarct dementia and Alzheimer's disease. In Sokoloff L (ed): Brain Imaging and Brain Function. Proceedings of the 62nd Annual Meeting of the Association for Research in Nervous and Mental Disease. New York, Raven, 1984
21. Loizou LA, Kendall BE, Marshall J: Subcortical arteriosclerotic encephalopathy: a clinical and radiological investigation. J Neurol Neurosurg Psychiatry 44:294–304, 1981
22. Naeser MA, Gebhardt C, Levine HL: Decreased computerized tomography numbers in patients with presenile dementia. Arch Neurol 37:401–409, 1980
23. Neumann M, Cohn R: Progressive subcortical gliosis, a rare form of presenile dementia. Brain 90:405–418, 1967
24. Okeda R: Morphometrische Vergleichsuntersuchungen an Hirnarterien bei Binswangerscher Encephalopathie und Hochdruckencephalopathie. Acta Neuropathol 26:23–43, 1973
25. Olszewski J: Subcortical arteriosclerotic encephalopathy. World Neurol 3:359–373, 1965
26. Pullicino P, Eskin T, Ketonen L: Prevalence of Binswanger's disease. Lancet 1:939, 1983
27. Romanul FCA: Examination of the brain and spinal cord. In Tedeschi CG (ed): Neuropathology, Methods and Diagnosis. Boston, Little, Brown, 1970, pp 131–214
28. Rosenberg GA, Kornfeld M, Stovring J, Bicknell J: Subcortical arteriosclerotic encephalopathy (Binswanger): computerized tomography. Neurology (NY) 29:1102–1106, 1979
29. Seitelberger F: Dementia following non-arteriosclerotic vascular processes of the CNS. In Meyer JS, Lichner H (eds): Cerebral Vascular Disease. St. Louis, Mosby, 1974, pp 200–226
30. Sternby NH: Atherosclerosis in a defined population. Acta Pathol Microbiol Scand Suppl 194, 1968
31. Svennerholm L: Distribution and fatty acid composition of phosphoglycerides in normal human brain. J Lipid Res 9:570–579, 1968
32. Tomonaga M, Yamanouchi H, Tohgi H, Kameyama M: Clinicopathologic study of progressive subcortical vascular encephalopathy (Binswanger type) in the elderly. J Am Geriatr Soc 30:524–529, 1982
33. Valentine AR, Moseley IF, Kendall BE: White matter abnormality in cerebral atrophy: clinicoradiological correlations. J Neurol Neurosurg Psychiatry 43:139–142, 1980
34. Zeumer H, Schonsky B, Sturm KW: Predominant white matter involvement in subcortical arteriosclerotic encephalopathy (Binswanger disease). J Comput Assist Tomogr 4:14–19, 1980