White Matter Lesions and Disequilibrium in Older People

II. Clinicopathologic Correlation

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Objective: To identify the cause of subcortical white matter lesions seen on magnetic resonance imaging in older patients with progressive deterioration of gait and balance.

Design: Postmortem examination of three patients with objective impairment of gait and balance thought to be due to subcortical white matter lesions identified on magnetic resonance imaging. Brain sections were stained with routine methods and for glial fibrillary acid protein using an immunoperoxidase technique.

Patients: Part of a prospective study of gait and balance problems in older people. None had a history of hypertension or discrete strokelike episodes.

Results: Other than a few small infarcts in the basal ganglia and internal capsule in the patient with the mildest gait disorder, there were no gross or microscopic features on routine examination post mortem to explain the white matter hyperintensities on magnetic resonance imaging or the progressive gait deterioration. By contrast, immunohistochemical staining with anti–glial fibrillary acid protein showed prominent astrocytosis T_2-weighted high-intensity signal areas on magnetic resonance imaging.

Conclusions: The astrocytes presumably swell as they take up extravasated protein at the site of a breakdown in the blood-brain barrier, and the increased water content per unit volume increases the magnetic resonance imaging proton signal. We hypothesize that the astrocytes may have been initially activated by small infarcts or subclinical ischemia, but the process then became self-perpetuating, ultimately involving most of the white matter and producing the severe gait disorder.

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BALANCE AND gait problems are common in older people, and associated falls are an important cause of morbidity and mortality.[1] Often, it is difficult to ascribe a specific cause for the balance disorder even after extensive clinical evaluation.[2] Periventricular white matter hyperintensities on magnetic resonance imaging (MRI) are also common in older people,[3-6] and some authorities have suggested that deep white matter lesions are an important cause of disequilibrium in older people.[7-9] We found that older patients with subjective and objective abnormalities of gait and balance have significantly more severe subcortical white matter hyperintensities on MRI than did age-matched control subjects.[10] Interruption of long loop reflexes that transverse the periventricular white matter could lead to impaired balance and increased likelihood of falls.[8,11] However, white matter high-intensity signal areas on MRI occur in older people who have normal balance.[5,6,10] No doubt, there are several pathophysiologic mechanisms for deep white matter high signal areas on MRI.

To further address these issues, clinical pathologic correlation was performed in three older patients who presented with slowly progressive imbalance and gait dysfunction, each having shown prominent deep white matter high signal areas on MRI before death. These patients underwent follow-up with regular examinations as part of a prospective study of dizziness and disequilibrium in older people. Each underwent a complete history and physical examination, including semiquantitative gait scores and quantitative posturography. Their gait exhibited features commonly seen in older people, and no specific cause for the gait and balance

neurologic examination was unremarkable. Quantitative visual-oculomotor and vestibulo-oculo motor function testing was within normal limits. An MRI scan revealed cortical atrophy, enlarged ventricles, and diffuse periventricular high-intensity signal areas.

Follow-up examinations over the next 3 years documented a progressive deterioration in her balance and gait such that, on the most recent examination before her death, she was unable to stand without assistance and could not take even a single step without support (**Table 1**). She tended to fall backward unless supported. A second MRI scan performed within a month of her death showed further progression of the diffuse periventricular high-intensity signal intensity areas (**Figure 1**, top left and top center).

CASE 2

Patient 2 initially presented at age 79 years complaining of dizziness and disequilibrium dating back about 2 years. He reported that he felt dizzy and insecure whenever he attempted to walk and that his dizzy sensation was relieved by sitting or lying down. He reported a throbbing sensation in his head when he attempted to walk, and this sensation persisted even after he sat down, although it would gradually disappear. His medical history was of note for a coronary bypass operation 10 years earlier and the recent recurrence of angina pectoris treated with nifedipine (Procardia). He had never been hypertensive. On examination, his gait was slightly wide-based, his stride length was decreased, and he turned slowly. He could not walk in tandem for even two steps. Mental status was normal, and the remainder of the findings on neurologic examination were unremarkable.

He entered our prospective study 5 years later, at which time he reported a definite deterioration in gait. He had several severe falls described by observers as "falling like a log" without any apparent attempt to catch himself. His base was widened, and he took small careful steps using a cane to help with balance. He turned en bloc, and there was loss of associated arm movements. Findings from the Mini-Mental State examination at that time revealed a score of 30 of 30. Visual acuity was 20/30 in both eyes, and, other than some mild decreased vibratory sense in the feet, his neurologic examination showed normal findings. Quantitative vestibular function testing documented significantly decreased vestibulo-ocular reflex gain to rotation at low frequencies (<0.2 Hz) but normal gain at higher frequencies. Follow-up examinations over the next 3 years documented a gradual progressive deterioration in his gait, but the score on the Mini-Mental State examination remained at 30. An MRI scan of the brain performed 5 months before his death due to a myocardial infarction showed extensive deep white matter high signal areas involving most of the subcortical white matter (Figure 1, top right and bottom left).

abnormality was identified other than the deep white matter lesions on MRI. Each exhibited a gradual progression of the gait impairment before dying of unrelated causes. At postmortem examination, we tried to characterize the nature of the white matter lesions.

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REPORT OF CASES

CASE 1

Patient 1 initially presented at age 92 years complaining of a gradual deterioration in balance and gait dating back to about age 80 years. She reported "a drunken feeling" when she was on her feet along with a pressure sensation at the top of her head. Her family noted a more recent gradual deterioration in memory and cognitive functions. She fell several times, fracturing an arm and then a hip. Her medical history revealed an abdominal aneurysm repair 10 years earlier and an aortic valve replacement and subclavian artery endarterectomy, performed in the prior year. She never had hypertension. On her

initial examination, she was able to walk with a slightly widened base, taking small slow steps as though her feet were anchored to the floor. She turned en bloc and tended to lose her balance on turns. Mental status examination showed a moderate global dementia. Visual acuity was 20/50 in both eyes and, other than cortical release signs and a modest decrease in vibration sense in the feet, her

CASE 3

Patient 3 entered the prospective study at age 82 years, reporting some mild imbalance particularly with rapid turns, which he noted was a definite change over the prior

Table 1. Mini-Mental State Examination Status, Tinetti Total Gait and Balance Scores, and Results of Static and Dynamic Posturography on Repeated Testing in Three Patients*

| Patient | Age, y | Mini-Mental State Score | Tinetti Score | Sway Velocity, mm/s† | | | | | |
| | | | | Static | | A-P Tilt | | M-L Tilt | |
				EO	EC	EO	EC	EO	EC
1	92	18	14	13.8	26.4	F	F	F	F
	93	13	8	16.2	30.2	F	F	F	F
	94	14	...‡	...‡	...‡	...‡	...‡	...‡	...‡
2	85	30	22	13.2	49.6	91.4	149.7	F	74.0
	86	30	17	35.7	69.3	116.8	174.7	66.7	118.4
3	82	28	26	18.4	20.7	62.9	65.2	32.3	41.6
	83	29	24	33.6	36.7	185.1	255.3	77.5	167.6
Normal mean	...	28	27	12.2	22.2	70.4	107.9	32.6	62.3
SD	...	1	2	4.9	14.2	23.0	30.9	14.2	26.6

*Normative data from age-matched control subjects.[12]

†A-P indicates anterior-posterior tilt of platform; M-L, medial-lateral tilt of platform; EO, eyes opened; EC, eyes closed; and F, patient was supported to avoid falling.

‡Could not stand without assistance.

year. His medical history revealed coronary bypass surgery 5 years earlier and recurrent angina pectoris. On his initial examination, his gait showed only some slight decrease in stride length and slow careful turns because of his concern about losing balance. He could take four or five steps in tandem before taking a sidestep. Results from the initial Mini-Mental State examination showed a score of 28 of 30. Quantitative visual-oculomotor and vestibulo-oculomotor testing showed normal findings.

Follow-up examination a year later showed slight but definite deterioration in his gait. The base was slightly widened, and the stride length diminished. He turned en bloc and was insecure when he attempted to make rapid turns. The remainder of the examination remained unchanged. An MRI scan of the brain at that time showed several discrete infarcts in the left deep white matter and also punctate deep white matter high-intensity signal areas scattered throughout the white matter (Figure 1, bottom center and bottom right). Three months after this second examination, the patient died of a massive myocardial infarction.

RESULTS

CLINICAL FEATURES

All three patients showed a gradual deterioration in gait and balance during the period of observation (Table 1). Patient 1 also had a deterioration in mental status, while patients 2 and 3 had normal mental status evaluations throughout. Quantitative posturography showed increased sway velocity for both static and dynamic tests compared with age-matched control subjects, and the sway velocity increased as the gait and balance disorder progressed (Table 1). Dynamic posturography could not be performed on patient 1, even on the initial examination, because of her severe imbalance.

All three patients had grade 2[10] deep white matter high-intensity signal areas on MRI (Figure 1). In patient 1, the entire subcortical white matter was diffusely involved without any distinct focal areas. In patient 2, there were multiple punctate high-intensity signal areas throughout. In some ar-

eas, there was a confluence of these punctate areas, giving a more diffuse pattern, similar to that of patient 1. Patient 3 had discrete localized high-intensity signal areas in the basal ganglia and internal capsule, suggesting localized infarction and multifocal T_2-weighted intense lesions throughout the deep white matter. None of the patients had clinical events suggesting acute stroke.

CLINICOPATHOLOGIC CORRELATIONS

Gross examination of the brains did not reveal an explanation for the high-intensity signal areas on MRI, other than the old infarcts in the left caudate and internal capsule in patient 3. Patient 1 died of a pontocerebellar hemorrhage (exact site of origin could not be ascertained) that grossly distorted the brain-stem structures. Other than this event, there were no gross findings in patient 1 or in patients 2 and 3 that could explain the progressive deterioration in balance and gait.

Routine microscopic examination also did not explain the clinical features in these patients or their MRI findings (Table 2). Infrequent small areas of infarction were identified in the deep white matter in patients 2 and 3, but no distinct areas of infarction were identified in patient 1. There were no cerebellar infarcts, and the brain stems of patients 2 and 3 were normal (as noted in patient 1, the brain stem was severely damaged by the terminal event). Changes that could be correlated with Alzheimer's disease were rare except for the finding of frequent senile plaques and neurofibrillary tangles in the temporal lobes in patient 2. This patient did not show signs of dementia on clinical testing. Arteriosclerotic changes in small vessels were common in the deep white matter in all three patients. In patient 1, arteriosclerotic changes with fibrous intimal hyperplasia were particularly prominent, involving nearly all meningeal vessels (Figure 2). The blood vessels were negative for amyloid.

MRI-PATHOLOGIC CORRELATIONS

To optimize radiographic-pathologic correlations, at the time of cutting the fixed brains, the slices themselves were
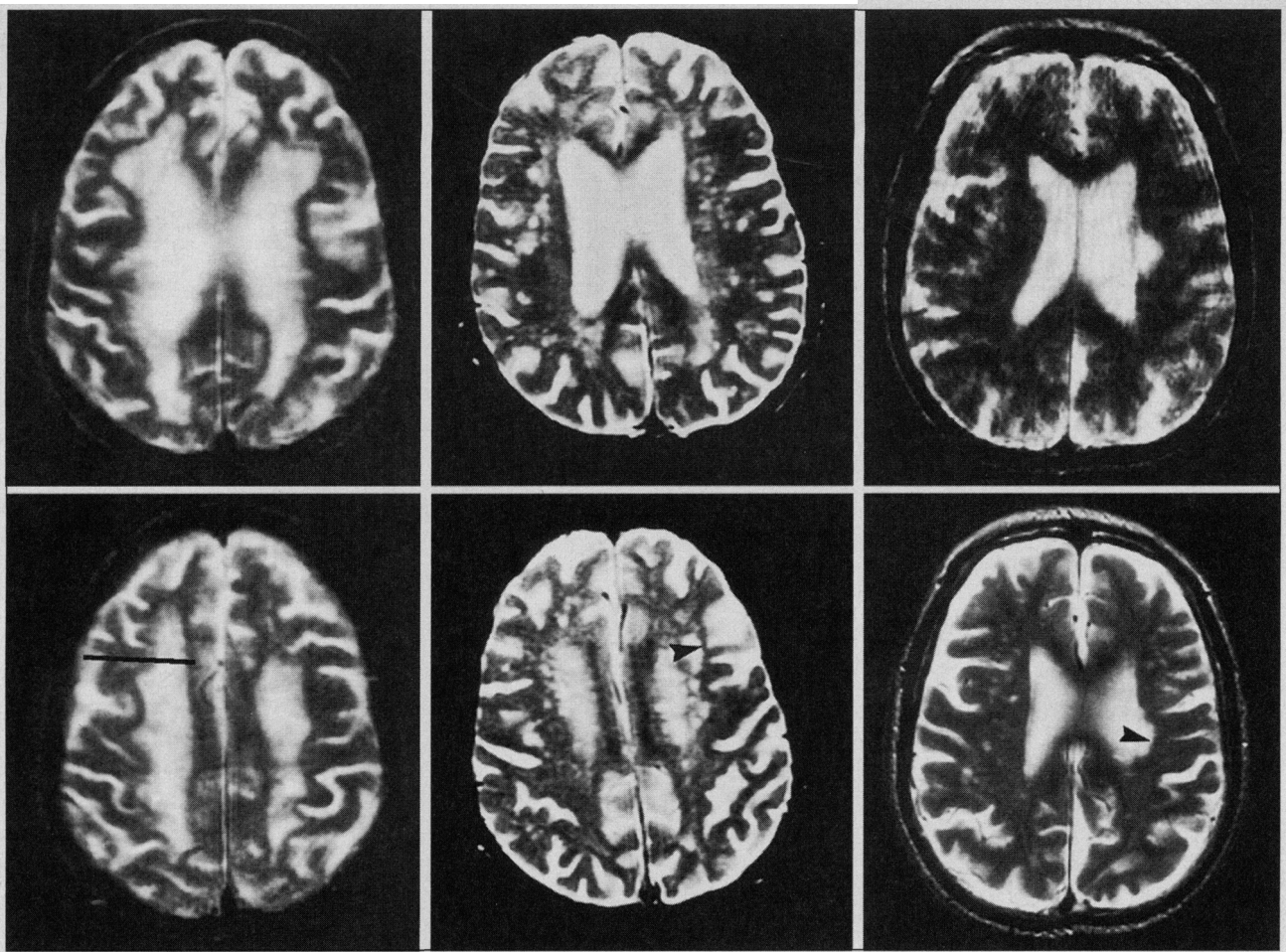
Figure 1. The T_2-weighted magnetic resonance imaging transverse sections of the brain in patient 1 (left, top and bottom), patient 2 (center, top and bottom), and patient 3 (right, top and bottom) showing subcortical white matter hyperintensities. The bar in the section shown at bottom left indicates the location of the frontal brain sections shown in Figure 3, left. The arrowhead right, top and bottom in the sections shown at right, top and bottom indicates the location of the sections shown in Figure 4.

Table 2. Summary of Pathologic Changes

| | Cortex | | | White Matter | | | Blood Vessels | |
Patient	Atrophy	Senile Plaques*	Neurofibrillary Tangles*	Microinfarcts	Demyelination	Astrocytosis	Arteriosclerosis	Atherosclerosis
1	Moderate-severe	Rare	Rare	None	Minimal	Diffuse, severe	Severe	Severe
2	Mild	Frequent† ~20/mm²	Frequent† ~15/mm²	Infrequent	None	Moderate to severe, patchy	Moderate	Moderate
3	Mild	Rare	Rare	Infrequent	None	Moderate, patchy	Mild	Moderate

*Assessed by Bielschowsky and Gallyas staining techniques.
†Mainly in temporal lobes.

photocopied and blocks were taken from precisely defined loci. The clearest MRI-pathologic correlations occurred with the infarcts seen in the left caudate and nearby deep white matter in patient 3. The discrete area on MRI correlated with cystic lesions that could be seen both grossly and microscopically. Myelin stains of the deep white matter showed relatively good preservation of myelin in all three patients (Table 2). In patient 1, who exhibited the most prominent deep white matter high-intensity signals, the myelin was remarkably preserved (**Figure 3**, left, top panel). The most dramatic feature

in patient 1 was the diffuse astrocytosis best demonstrated with the glial fibrillary acid protein (GFAP) stains. Reactive astrocytes were present in large numbers throughout the deep white matter despite the absence of any localized areas of infarction (Figure 3, left, middle panel). The deep white matter was essentially a sheet of activated astrocytes (Figure 3, center and right). On the other hand, there were few activated astrocytes in the cortex, so that there was a sharp boundary at the white matter–cortical junction on the GFAP stains (Figure 3, left, middle panel, and center), corresponding with the sharp

boundary on the T_2-weighted high-intensity signal on MRI (Figure 1, top left and top center). Patients 2 and 3 exhibited patchy astrocytosis in the deep white matter consistent with the white matter high-intensity signal areas on MRI (**Figure 4**).

Did the white matter lesions identified on MRI and at postmortem examination cause the gait abnormalities seen in our three patients? No other cause was found after extensive clinical evaluation and complete examination of the brain. Patient 2 had decreased vestibulo-ocular responses at low frequencies of rotation compared with age-

Figure 2. *Section showing marked degree of eccentric fibrous intimal hyperplasia of leptomeningeal (medium-sized) artery in patient 1 (Kluver-Barrera stain, ×205). Note foamy astrocytes in the hyperplastic intima.*

matched control subjects, but the degree of his balance and gait disorder was much greater than we have seen in other patients with bilateral vestibular loss.[2] Of course, the vestibular loss could have contributed to his imbalance and gait dysfunction. It seems inappropriate to assign a specific pattern of gait disorder to periventricular white matter disease, even to the diffuse involvement seen with Binswanger's disease, since the pattern of disequilibrium depends on the location of the lesions rather than on the pathophysiologic findings. Early multifocal involvement such as that seen in patient 3 could produce a wide range of gait disorders depending on what structures are involved.[16] On the other hand, severe diffuse involvement such as that seen in patient 1 produces an end-stage pattern such as the "lower-half parkinsonism" of Thompson and Marsden.[11] All three patients had lesions involving the afferent and efferent interconnections of the leg areas of the motor and supplementary motor areas of the cortex with the thalamus and basal ganglia.

MRI-PATHOLOGIC CORRELATIONS

Most of the prior studies correlating MRI images with histopathologic findings have used MRI scans obtained post mortem.[17-19] One study that imaged a patient's brain while alive and again post mortem found the same white matter hyperintensities in both studies, indicating that postmortem MRI studies are valid.[18] There is general agreement that the white matter hyperintensities seen on MRI have multiple pathologic correlates. Although these lesions resemble the MRI findings in multiple sclerosis, they usually do not represent demyelination. Grafton et al[19] found that myelin and axon stains showed varying de-
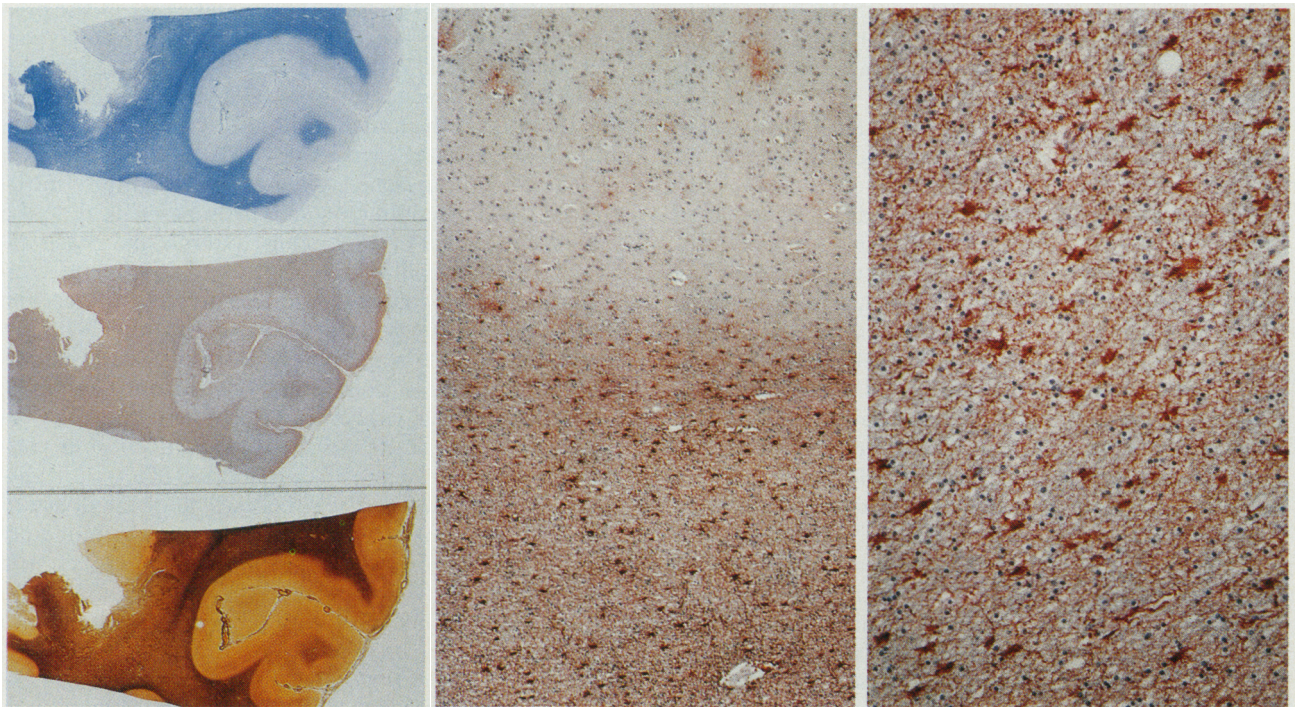

Figure 3. *Left, Frontal brain sections from patient 1 taken at the level of the bar in Figure 1, bottom left, stained with Kluver-Barrera (top), glial fibrillary acid protein (GFAP) (middle), and Bielschowsky (bottom). Center and right, Microscopic views of the white matter–cortical junction (×85) (cortex is at right of the section) (center) and the deep white matter (×230) (right) from the GFAP-stained section show the diffuse astrocytosis of the white matter with relative sparing of the cortex.*
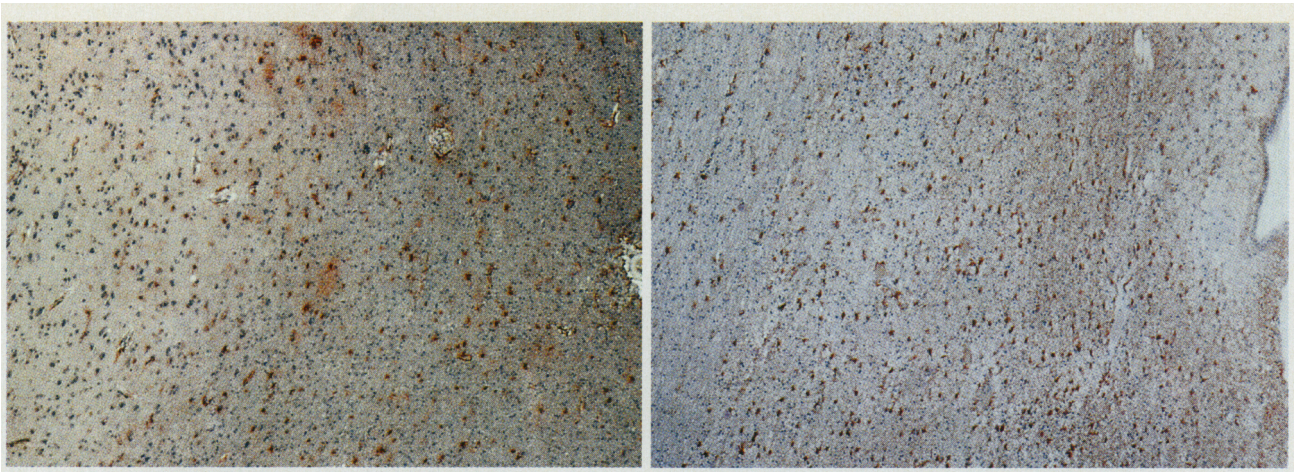
Figure 4. *Microscopic sections from patient 2 (left) and patient 3 (right) stained with glial fibrillary acid protein from area shown with the arrowhead in Figure 1, right, top and bottom. In the illustration at the left, the cortex is at the left, and white matter is at the right. In the illustration at the right, the ventricle is at the far right. Note the diffuse astrocytosis of the white matter (×90).*
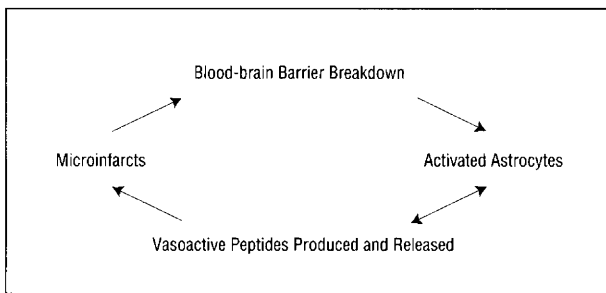

Figure 5. *Proposed mechanism for subcortical white matter lesions.*

grees of diffuse pallor in many areas of white matter examined, but these areas of pallor occurred both within and without areas of high-intensity signal on MRI scans. They concluded that neither the myelin nor the axon stains showed discrete white matter abnormalities that corresponded to the MRI findings. Some of the periventricular white matter hyperintensities on MRI represent distinct brain infarctions. These infarcts typically consist of a central necrosis with surrounding astrocytic reaction. The GFAP stains showed not only reactive astrocytes around the infarct but swollen astrocytes extending along the myelin sheaths for several centimeters from the center of the infarct, so-called isomorphic gliosis. The cause of the high-intensity signal on MRI in areas without clear infarcts is more controversial. Awad et al[17] suggested that age and hypertension result in dilatation of perivascular spaces and that these spaces fill with water and cause an increase in the proton MRI signal. In other words, the MRI lesions reflect "wear and tear" in the brain parenchyma that occur with aging and chronic cerebrovascular disease. Aging and hypertension also lead to hyaline sclerosis and ectasia of the small arteries and arterioles, which eventually can lead to a multi-infarct state such as that seen with Binswanger's disease.

Astrocytic gliosis was the likely cause of the white matter hyperintensities on MRI in our patients. Activated swollen astrocytes increased the water content per unit volume and thus increased the MRI proton signal.[18] Others have suggested that activated astrocytes contribute to the abnormal MRI signal in the plaques of chronic multiple sclerosis,[20] and, as noted above, reactive astrocytes surrounding a focal area of infarction increase the size of the hyperintensity seen on MRI.[18] Our patient 1 had remarkable diffuse astrocytosis with reactive astrocytes occurring in sheets throughout the white matter. When stained for GFAP with an immunoperoxidase technique, the swollen bodies and processes of the reactive astrocytes were readily apparent (eg, Figure 3, right).

A UNIFYING THEORY

A unifying theory to explain progressive diffuse deep white matter disease such as that seen in our patients 1 and 2 is illustrated in **Figure 5**. The initial event in the process is a breakdown in the blood-brain barrier. Hypertension, diabetes, and, possibly, even normal aging lead to hyalinized changes in arterioles, eventually leading to obliteration of the lumen and small infarcts. Breakdown in the blood-brain barrier may occur in areas of ischemia even without infarction. Brun and Englund[21] introduced the concept of "incomplete infarcts" to describe areas with loss of myelin, axons, and reactive gliosis associated with hyalinized changes in the arterioles but without the necrosis characteristic of a complete infarct. The reactive astrocytosis in these areas of incomplete infarct were similar to the isomorphic gliosis seen near the boundary regions of infarcts. Of interest, Brun and Englund[21] found incomplete infarcts in 60% of patients with Alzheimer's disease, and the degree of these deep white matter changes correlated with the clinical severity of the disease. None of our patients had pathologic evidence of Alzheimer's disease, though patient 2 showed moderate numbers of senile plaques in the temporal cortex, and only patient 1 had dementia.

Astrocytes become activated after a breakdown in the blood-brain barrier as serum proteins enter the extracellular fluid of the brain and are taken up by the astrocytes, presumably to detoxify the extracellular environment.[18] The intracellular fluid content of the astrocyte is markedly increased, leading to an increased proton signal on MRI. Zhang et al[22] recently showed that reactive

astrocytes in the deep white matter of patients with subcortical infarcts are immunolabeled with endothelin-1 antiserum, thus indicating an increased content of endothelin-1, a potent and long-lasting vasoconstrictor peptide.[23] Release of endothelin and other vasoactive peptides from the astrocytes into the microenvironment of the brain could lead to constriction of small vessels. This, in turn, could lead to microinfarcts, a further breakdown in the blood-brain barrier, and further activation of astrocytes. Subtle structural abnormalities of the blood-brain barrier have been found in white matter microvessels with advancing age.[24] In addition, these peptides themselves may stimulate further gliosis. Administration of endothelins to cultures of astrocytes promotes mitogenesis and enhanced phospholipid turnover.[25] Presumably, cortical astrocytes are more resistant to this process of activation than are astrocytes in the white matter.

A rare but important familial disorder that may provide important clues to the pathogenesis of the deep white matter lesions so common in older people is the hereditary multi-infarct syndrome, so-called cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL).[26,27] This autosomal dominant disorder is characterized by strokelike episodes leading to progressive dementia and gait deterioration in young to middle-aged adults. Examination of the brains in patients who died of CADASIL show changes similar to those seen in patients with arteriosclerotic encephalopathy (Binswanger's disease).[28,29] There is hyalinized degeneration of the arterioles in the absence of hypertension, areas of discrete infarct confined to the white matter, and diffuse astrocytosis with activated astrocytes documented with GFAP stains. Zhang et al[22] showed that the reactive astrocytes in hereditary multi-infarct disease expressed endothelin-1, similar to the reactive astrocytes associated with nonhereditary multi-infarct syndromes. Recently, genetic linkage analysis in two families with CADASIL identified the disease locus on chromosome 19q12.[30] An abnormal protein could lead to inappropriate activation of astrocytes or, possibly, to inappropriate endothelin production in otherwise normal astrocytes. This, in turn, would lead to multiple infarcts of the deep white matter and the progressive loss of neurologic function.

A role for activated astrocytes and endothelin in the production of subcortical white matter lesions has important therapeutic implications. Recently, endothelin receptor antagonists have been developed, including an orally active nonpeptide antagonist of endothelin receptors.[31] If the above theory is correct, one would expect these endothelin antagonists to be effective in patients with CADASIL and Binswanger's disease. These drugs might also be effective in older patients with progressive white matter disease without hypertension, such as the three patients described in this study.

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