PATCHY FOCI of increased signal intensity are frequently identified on magnetic resonance imaging (MRI) in the elderly. While some of these foci correspond to known or suspected pathologic processes, most are unexpected or incidental. In an accompanying report, incidental subcortical MRI lesions in the elderly were shown to be associated with arteriosclerosis, dilated perivascular spaces, and vascular ectasia (*p* < 0.05). These histological changes were characteristic of "état criblé" which, like subcortical MRI lesions, is associated with age and hypertension. Shrinkage (or atrophy) of the brain parenchyma around ectatic blood vessels would result in an extensive network of tunnels filled with extracellular water. The proton MRI signal from such areas of the brain would be increased. Gliosis and small areas of infarction occasionally coexisted with "état criblé," but these were not present in all areas with MRI lesions and could not be distinguished by MRI signal alone. In conclusion, clinical and pathological correlations lend support to the uniform hypothesis that MRI provides a nonspecific index of brain parenchymal alterations caused by aging and chronic cerebrovascular disease.

**Patients and Methods**

The patients represented consecutive cases over 60 years of age, who died of nonneurologic causes, and who underwent postmortem examination at the Barrow Neurological Institute. Cases with known demyelinating disease, known structural brain pathology, or previous brain surgery were excluded.

The MRI was performed eleven days postmortem on case 7, and could not be repeated after death for technical reasons. The case was included in this report because of the severity of MRI findings, and the short interval between the scanning and death. In all other cases, the MRI was done postmortem on the fixed brain just prior to pathological examination. In addition, MRI was also performed in the fresh state (prior to fixation) in cases 5 and 6.

**Technique of Postmortem MRI**

The brain was harvested at autopsy and was suspended from the falx cerebri in a cylindrical Tupperware™ container small enough to fit within the head holder compartment of the MRI system. Isotonic saline chilled to 4°C immersed the freshly harvested brain. Ventricular air acquired during brain removal was evacuated through the foramina of Lusck a and...
MRI IN THE ELDERLY: II. PATHOLOGICAL CORRELATIONS/Awad et al

Magenie by tilting of the specimen. This suspension and immersion technique was necessary to prevent distortion or deformation of the brain. The container was oriented in the head holder allowing the falx cerebri to align precisely with the sagittal scanning plane.

Imaging was performed using a 1.5 Tesla superconductive unit manufactured by General Electric Corporation. Scanning was done in the axial, sagittal, and coronal planes with sections 5 mm thick and a scanning time of approximately 45 minutes. A multiple spin-echo protocol was used, identical to that used for routine clinical studies. Parenchymal foci of increased signal intensity were identified on the $T_2$ weighted scans, and were localized in at least two planes.

Immediately after completing the MRI scans in the fresh state, the saline solution was replaced by a phosphate buffered saline solution containing 10% formaldehyde and 1% methyl alcohol. The suspended brain was fixed by immersion for 10 to 14 days.

On the day preceding brain cutting, the MRI scan was performed on every specimen while still immersed in the formaldehyde solution. Identical scanning protocols were used, identifying and localizing the MRI lesions in the fixed brain. A software localizing grid and cursors allowed the determination of precise coordinates for each MRI lesion and the optimal brain cutting plane for each specimen.

Brain Cutting and Pathologic Examination

The fixed brain was cut in the appropriate plane using the MRI images (in three dimensions) as guiding maps. These images provided a wealth of topographic and internal anatomic detail sufficient to guide an experienced neuropathologist (PCJ) through the cutting of the specimen. The section of interest could be verified by the precise localization of anatomical structures seen on the corresponding MRI slice, e.g. one could easily verify the size and shape of the ventricular system, the precise pattern of gyri and sulci, and the size and shape of deep structures including the fornix, thalamus, and basal ganglia, etc. Since all MRI lesions were localized in two or more imaging planes and usually on more than one slice, they were unlikely to be "missed" with this anatomically guided sectioning technique.

Photographs of the gross sections were obtained for documentation of the macroscopic findings. Slices (15 mm x 15 mm x 2 mm) were excised from areas harboring MRI lesions. Similar slices were excised from control areas in the same brain (areas not harboring MRI lesions). The control slices were preferably sampled from contralateral or homologous zones, unless those areas also harbored MRI lesions. The slices were embedded in paraffin and were given a random code. Contiguous sections of each slice were stained with hematoxylin and eosin (H&E) for routine histological examination, with Luxol's fast blue (LFB) for myelin, and with glial fibrillary acidic protein (GFAP) stain for astrocytes and their processes.

The coded sections were examined by a single neuropathologist (PCJ) in a blinded fashion. The histological findings from each slice were recorded on a standardized sheet. The following specific changes were graded as none, mild, or severe: parenchymal

| Table 1 Clinical Background and Cause of Death in Eight Patients Undergoing Postmortem MRI Correlations |
|---|---|---|---|
| Age/sex | Pertinent past medical history | History of most recent illness | Cause of death |
| 1 | 84/F | Unremarkable | 1 month history of anorexia and weight loss | Acute renal failure |
| 2 | 61/M | Diabetes mellitus, coronary artery disease | Unstable angina | Myocardial infarction |
| 3 | 64/F | Sjogren syndrome, proteinuria, coronary artery disease | Angina | Ventricular arrhythmia, possible sepsis, renal failure |
| 4 | 75/M | Hypertension, TIA, abdominal aortic aneurysm | Abdominal mass | Myocardial infarction (hours after excision of benign abdominal mass) |
| 5 | 64/M | COPD, cardiac arrhythmia | Chronic respiratory failure | Congestive heart failure, cardio-pulmonary decompensation |
| 6 | 65/M | Hypertension, TIA, femoral occlusive disease | Intermittent claudication | Myocardial infarction (1 day after lumbar sympathectomy) |
| 7 | 79/F | Systemic lupus erythematosus, TIA | Transverse myelitis of cervical cord | Acute renal failure |
| 8 | 82/M | Hypertension, diabetes mellitus, dementia, coronary artery disease | Died in nursing home | Myocardial infarction |

*TIA: transient ischemic attack; COPD: chronic obstructive pulmonary disease.
TABLE 2  Histopathological Correlation of Subcortical MRI Lesions in the Elderly

<table>
<thead>
<tr>
<th></th>
<th>Areas without MRI lesions n = 15</th>
<th>Areas with MRI lesions n = 27</th>
<th>Chi-square comparison p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial and arteriolar sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>12 (80%)</td>
<td>7 (26%)</td>
<td>0.190</td>
</tr>
<tr>
<td>mild</td>
<td>3 (20%)</td>
<td>8 (30%)</td>
<td>0.699</td>
</tr>
<tr>
<td>severe</td>
<td>0 (0%)</td>
<td>12 (44%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Arterial and venous ectasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>9 (60%)</td>
<td>4 (14.8%)</td>
<td>0.280</td>
</tr>
<tr>
<td>mild</td>
<td>2 (13.3%)</td>
<td>6 (22.2%)</td>
<td>0.592</td>
</tr>
<tr>
<td>severe</td>
<td>4 (26.7%)</td>
<td>17 (77%)</td>
<td>0.251</td>
</tr>
<tr>
<td>Dilated perivascular spaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>12 (80%)</td>
<td>2 (7.4%)</td>
<td>0.082</td>
</tr>
<tr>
<td>mild</td>
<td>2 (13.3%)</td>
<td>9 (33.3%)</td>
<td>0.497</td>
</tr>
<tr>
<td>severe</td>
<td>1 (6.7%)</td>
<td>16 (59.3%)</td>
<td>0.162</td>
</tr>
<tr>
<td>Combination of above changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe form of one or more above changes</td>
<td>4 (26.7%)</td>
<td>27 (100%)</td>
<td>0.033*</td>
</tr>
<tr>
<td>severe form of two or more above changes</td>
<td>1 (6.6%)</td>
<td>23 (85%)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Pallor to myelin stains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>15 (100%)</td>
<td>2 (7.4%)</td>
<td>0.034*</td>
</tr>
<tr>
<td>mild</td>
<td>0 (0%)</td>
<td>19 (70.4%)</td>
<td>0.162</td>
</tr>
<tr>
<td>severe</td>
<td>0 (0%)</td>
<td>6 (22.2%)</td>
<td>0.411</td>
</tr>
<tr>
<td>Gliotic reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>14 (93.3%)</td>
<td>11 (40.7%)</td>
<td>0.162</td>
</tr>
<tr>
<td>mild</td>
<td>1 (6.7%)</td>
<td>12 (44.4%)</td>
<td>0.293</td>
</tr>
<tr>
<td>severe</td>
<td>0 (0%)</td>
<td>4 (14.9%)</td>
<td>0.532</td>
</tr>
<tr>
<td>Other or unexpected pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lacunar infarction</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>capillary telangiectasia</td>
<td>1 (6.7%)</td>
<td>1 (3.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level.

edema, enlarged perivascular spaces, lacunar infarction, tract degeneration, gliosis, inflammation, macrophage infiltration, arteriosclerosis or hyalinosis, arterial or venous ectasia, and myelin pallor. In addition, specific comments on the above changes or on other histologic findings were noted at the discretion of the examining pathologist.

Data Analysis

The slice code was subsequently broken, and each slice was identified as to patient, area of origin, and corresponding MRI findings. Descriptive clinical-radiological-pathological correlations were formulated. In addition, a computer assisted analysis was conducted correlating specific histological features with the presence of MRI lesions. The Chi-Square test was used in each instance with 1 df and Yates’s continuity correction.

Results

There were three females and five males ranging in age from 61 to 84 years (mean = 72 years). The clinical background and cause of death for each case are summarized in Table 1. The brain weights at autopsy ranged from 1140 g to 1790 g (mean = 1355 g). Four patients had a previous history of ischemic cerebrovascular disease: 3 were hypertensive, and 3 had transient ischemia without persisting neurologic signs or symptoms. The fourth patient (case 8) had multiinfarct dementia (by clinical criteria). All patients died of nonneurologic causes, and none had a final hospitalization of more than eleven days. No patient was on a ventilator for more than 24 hours before death.

Prevalence and Distribution of MRI Lesions

Incidental MRI lesions were encountered in every case (fig. 1). In both instances where MRI was performed before and after brain fixation, MRI lesions were identical in the fresh and fixed states (fig. 2). All the incidental MRI lesions were subcortical. They most frequently involved the white matter adjacent to the frontal horns of the lateral ventricles (6 cases). Other frequently involved areas included the white matter of the optic radiations (5 cases), the basal ganglia (3 cases), and the centrum semiovale (2 cases). Lesions occasionally formed large patches involving...
MRI IN THE ELDERLY: II. PATHOLOGICAL CORRELATIONS

MRI FINDINGS IN EIGHT ELDERLY PATIENTS SUBMITTED TO POSTMORTEM EXAMINATION

Case #1  84 F
Case #2  61 M
Case #3  64 F
Case #4  75 M
Case #5  64 M
Case #6  65 M
Case #7  79 F
Case #8  82 M

*MRI done 11 days pre-mortem

FIGURE 1. Anatomical distribution of subcortical MRI lesions in 8 elderly patients. In all but case 7, the findings are those noted on postmortem MRI of the fixed brain. The sections selected are those best highlighting the lesions.

FIGURE 2. Postmortem in vitro MRI of case 6. (A) scan performed in the fresh state (in saline); (B) scan performed in the fixed state (in formalin). In each instance, the upper rows show "slightly $T_2$ weighted" images (TR = 2 seconds, TE = $25 \times 10^{-3}$ seconds) and the lower rows show "heavily $T_2$ weighted" images (TR = 2 seconds, TE = $80 \times 10^{-3}$ seconds). Bilateral frontal and occipital periventricular MRI lesions are noted in the fresh and fixed states.

the deep gray nuclei and adjacent white matter. No MRI lesion corresponded to a clinical neurological deficit or was suspected to be present during life.

Findings on Gross Pathological Examination
Remarkably few gross abnormalities were noted in the areas corresponding to the MRI lesions (figs. 3 and 4). Subtle grayish discoloration was noted in the angles of the lateral ventricles in 6 cases, and involved areas of MRI lesions in every instance. An indistinct sieve-like appearance of the brain parenchyma was noted in all cases and seemed to correspond to areas involved by MRI lesions. On loupe magnification, these sieve-like areas represented prominent vessels and/or perivascular space within the parenchyma. One small area of lacunar infarction (2 mm) was identified in the right thalamus of case 8. Capillary telangiectasias could be visualized on gross examination of two other cases. The lacunar infarction and one telangiectasia corresponded to areas with MRI abnormality. The second telangiectasia (3 mm) involved a cortical gyrus, but did not present an abnormal signal on MRI.

Findings on Histological Examination (table 2)
Forty-two slices were sampled for histological examination. Twenty-seven corresponded to areas with MRI lesions, and 15 corresponded to areas without MRI lesions (control areas). Dilated perivascular spaces, vascular ectasia, and arteriosclerosis were found more frequently in MRI positive areas (figs. 5–7). A severe form of one or more of these alterations was found in 27 of 27 MRI positive regions and in 4 of 15 control regions ($p < 0.05$). A severe form of two or more of these vascular changes was found in 23 of 27 MRI positive areas and in 1 of 15 control areas ($p < 0.05$).

In addition to the vascular changes noted above, there were other pathological alterations in some of the areas corresponding to MRI lesions. Patchy zones of gliosis were encountered in 16 of 27 areas with MRI
abnormality (and in 1 of 15 control areas). Gliosis was limited to subependymal white matter (fig. 5) and to the zone surrounding a lacunar infarction. Pallor to myelin stains was observed in the same areas exhibiting gliosis. Unlike demyelinating disease, severe pallor to myelin stains was not associated with axonal preservation or perivascular inflammation. Instead, it occurred in conjunction with loss of myelinated fibers and gliosis. All areas exhibiting pallor to myelin stains and gliosis also demonstrated dilated perivascular spaces, vascular ectasia, and arteriosclerosis.

Only one area of true infarction, a 2 mm lacune, was noted. It was surrounded by gliosis and myelin loss several millimeters beyond the zone of true brain necrosis. Aside from an incidental telangiectasia in one other case, there were no additional pathological findings corresponding to the MRI lesions.

Discussion

Subcortical foci of increased signal intensity are frequently identified on MRI in the elderly. While these lesions are associated with age, hypertension, and a prior history of brain ischemia, their clinical significance remains speculative. Furthermore, it is not known if any pathologic changes are responsible for the increased MRI signal in these lesions.

Conventional clinical-radiological-pathological correlations have been performed on patients with clinical evidence of advanced subcortical ischemic disease, who harbor such MRI lesions. These studies do not explain similar MRI findings in asymptomatic elderly patients. In asymptomatic cases, accurate pathologic correlations require that each patient would have died of nonneurologic causes shortly after an MRI scan revealed incidental lesions. This scenario is quite unlikely and imposes an additional selection bias. We have only encountered one such case in over two years of clinical MRI experience. Pathological correlations of MRI findings in this patient (case 7) were included in this study.

An alternative approach to the problem was to identify the MRI lesions on postmortem MRI scans. The technique of postmortem in vitro MRI has not been described previously. It provided images of comparable quality to those routinely obtained from the living brain using identical scanning protocols. Fixation of the brain did not impair the overall quality of imaging, the resolution of internal anatomical structures, or the appearance of subcortical parenchymal lesions. In all cases, the lesions were identified on the fixed brain just prior to sectioning, and precisely localized for pathological examination. The examination was performed in a blinded fashion, including control areas from the same specimen.
The MRI lesions involved the white matter adjacent to the lateral ventricles, the optic radiations, the basal ganglia, and the centra semiovale in decreasing frequency. The lesions were associated with a spectrum of histological alterations. Enlarged perivascular spaces and ectasia of small arteries and veins were found in all areas with MRI lesions regardless of anatomical location. These vascular changes were often associated with mild pallor to myelin stains and arteriosclerosis. A fraction of the lesions exhibited a more severe pathological process consisting of degeneration of myelinated axons and gliosis. The latter were limited to subependymal areas and the area surrounding a small lacunar infarction. The MRI signal did not differentiate between the milder form of histological changes (enlarged perivascular spaces and vascular ectasia) and the more severe form (myelinated fiber loss and gliosis).

**FIGURE 4.** (A) Premortem MRI of case 7. At the time of the scan, the patient had neck pain, mild cervical myelopathy (level at C5-C6), and normal mental status. The patient died 11 days later of renal failure. (B) Gross section of the fixed brain from the same case. Note the subtle grayish discoloration (straight arrows) and the diffuse sieve-like appearance of the parenchyma (curved arrows).

**FIGURE 5.** (Left): Photomicrograph of the right occipital periventricular area of case 4, in an area devoid of MRI lesions. Note the normal (narrow) perivascular space, and the absence of vascular ectasia and arteriosclerosis. (H & E; × 20). (Right): Photomicrograph of the right frontal periventricular area of the same case corresponding to the MRI lesion illustrated in figure 1. Note the dilated perivascular spaces (evident as prominent halos around small and large vessels), vascular ectasia, and sclerosis of arteries and arterioles. In addition, there is a patchy zone of gliosis (confirmed by GFAP stain) and degeneration of myelinated axons (confirmed by myelin stain) in the subependymal area (arrow) (H & E; × 20).

**FIGURE 6.** High magnification photomicrograph of the right frontal periventricular area of case 4 corresponding to the MRI lesion noted in Figs. 1 and 5B. Note the dilated perivascular spaces (evident as prominent halos around small and large vessels), and arteriosclerosis (curved arrows). (H & E; × 40).
The pathological substrate responsible for the increased MRI signal is subject to much controversy. Since similar MRI lesions are found in patients with multiple sclerosis, one might speculate that demyelination is responsible for the MRI abnormality. However, severe pallor to myelin stains was encountered in only a fraction of the MRI lesions. Also, myelin loss cannot account for MRI lesions involving gray nuclei. Furthermore, recent evidence suggests that myelin contributes little to the MRI signal at 1.5 Tesla, and that the difference in signal intensity between white and gray matter may result from differences in water content and distribution.\(^3,12,14\)

Gliosis is another potential cause of altered MRI signal. The replacement of myelinated axons by astrocytic processes may increase the water content per unit volume, and has been suggested as the cause of abnormal MRI signal in chronic multiple sclerosis plaques.\(^9,12,14\) In this study, the MRI signal was in fact increased in all areas affected by gliosis. However, gliotic proliferation was not present in all areas with MRI abnormality and could not account for all MRI lesions.

Vascular ectasia and dilated perivascular spaces were found in all areas with increased MRI signal and were significantly less common in control areas. These changes reflect shrinkage or atrophy of the brain parenchyma around blood vessels\(^9,13,16\) and result in an extensive network of tunnels filled with extracellular water (fig. 8). The proton signal would be increased in areas with such alterations.

The above changes in brain parenchyma have long been known to affect the aging brain. In 1843, Durand-Fardel described “numerous canals or small round holes in the cerebral tissue, from each of which a small vessel projected, and which were located in the striatum, thalamus, and cerebral white matter.”\(^9\) He referred to these changes as “état criblé,” a French expression meaning “riddled with shot or sieve-like.” Microscopically, the parenchyma is characterized by sclerosis of small arteries and arterioles, vascular ectasia, and dilated perivascular spaces.\(^9,10,13,16\) This state is usually asymptomatic and is associated with advancing age and hypertension.\(^6,9\) It is not to be confused with “état lacunaire,” the state of multiple subcortical frank lacunar infarctions manifested clinically asBinswanger’s disease or multi-infarct dementia.\(^9,10,13,16\) Because of their associations with cerebrovascular risk factors, “état criblé” and lacunar infarctions may coexist.\(^6,9,10\)

The clinical associations of subcortical MRI lesions in the elderly and the pathological correlates of these lesions lend support to a uniform hypothesis. We propose that these MRI lesions reflect “wear and tear” in the brain parenchyma which accompany aging and chronic cerebrovascular disease (fig. 9). Such “wear and tear” might be limited to “état criblé” in its earliest stages, and would likely be asymptomatic. In later stages there would be progression of the “état criblé” and accumulation of lacunar and non-lacunar infarctions, accompanying the clinical spectrum of symptomatic cerebrovascular disease. “État criblé” and subcortical infarctions are difficult to distinguish by MRI appearance alone, and often coexist.

Half a century ago, angiography opened the door to the identification of asymptomatic large vessel disease. In the 1970s, CT scanning provided the ability to diagnose small and clinically occult infarctions. For the first time, MRI may now enable the clinician to identify parenchymal alterations of aging and chronic cerebrovascular disease during life. Heretofore, the extent and distribution of such changes were not noted until the first clinical manifestations of stroke, or the examination of a neuropathologist. The natural history and clinical significance of these changes remain to be elucidated. Prospective follow-up of asymptomatic elderly patients with subcortical MRI lesions is currently underway at this institution.
Magnetic resonance imaging in the elderly: II. Pathological correlations

- **SYSTEMIC Atherosclerosis** (Coronary Disease, Carotid Disease, etc.)
- **AGING** Hypertension (Other Risk Factors)
- **MULTINFARCT STATE** ("Lacunar" Lesions, "Binswanger's Disease")
- **HYALINE Sclerosis and Aetiology of SMALL Arteries and ANEURYSMS" ("Isolated"
- **SYMPTOMATIC CEREBROVASCULAR DISEASE"

**FIGURE 9.** Schematic diagram illustrating a spectrum of chronic cerebrovascular disease. There is a gradual appearance of subcortical MRI lesions as the patient ages and risk factors accumulate. Subcortical MRI lesions increase as the various clinical manifestations of cerebrovascular disease become evident. The end stage of the process involves severe MRI lesions and a clinical form of the multi-infarct state.

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