Incidental Subcortical Lesions Identified on Magnetic Resonance Imaging in the Elderly. I. Correlation With Age and Cerebrovascular Risk Factors

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SUMMARY Patchy subcortical foci of increased signal intensity are frequently identified on magnetic resonance imaging (MRI) in the elderly. The incidence and clinical correlates of these lesions remain unknown. In this report, 240 consecutive MRI scans performed over a 6-month period were reviewed (excluding patients with recent brain trauma or known demyelinating disease). Subcortical incidental lesions (ILs) were identified, which could not be accounted for by the patient's current clinical diagnosis, neurological status, or CT scan. The ILs were graded according to size, multiplicity, and location. The incidence and severity of ILs increased with advancing age (p < 0.0005). Among patients over 50 years of age, the incidence and severity of ILs were correlated with a previous history of ischemic cerebrovascular disease (p < 0.05) and with hypertension (p < 0.05). Multivariable regression analysis identified age, prior brain ischemia, and hypertension as the major predictors of ILs in the elderly. Diabetes, coronary artery diseases, and sex did not play a significant role. With the exception of cerebrovascular disease, there was no association between ILs and any particular clinical entity, including dementia. It is concluded that subcortical parenchymal lesions are frequent incidental findings on MRI in the elderly, and may represent an index of chronic cerebrovascular diseases in such patients.

MAGNETIC RESONANCE IMAGING (MRI) of the brain has become a recognized and increasingly popular diagnostic modality. Unprecedented spacial resolution, flexibility in imaging, and the lack of ionizing radiation have all contributed to its widespread use. Furthermore, MRI has proven to be highly sensitive to subtle changes in brain parenchyma which accompany a wide variety of neurologic disorders.1 3 4 7 11-13 17 18 Such sensitivity has already found practical application in the screening of patients for multiple sclerosis.12 14 Conversely, the lack of specificity of MRI has limited its clinical usefulness in the presence of unexpected or incidental lesions.1 3 14 15 17

Patchy parenchymal lesions are frequently identified on MRI in the elderly.1 3 14 16 17 They are usually subcortical and multiple, and exhibit increased signal intensity on T2 weighted images. Lesions of this nature have been described in conjunction with known cerebrovascular disease, but are difficult to correlate with previous symptoms.1 3 17 Similar lesions have been reported in association with dementia,3 11 and in asymptomatic elderly patients.3 17 While there has been much speculation about the nature of such lesions, little is known about their clinical significance, prevalence in various age groups, or pathologic correlates.

In this report, a definition and a grading scheme for incidental MRI lesions are proposed, and their incidence and clinical associations are examined in 240 consecutive patients undergoing MRI at our institution. Multivariable regression analysis is used to determine the impact of age and cerebrovascular risk factors on the incidence and severity of these lesions. In an accompanying report, the pathological correlates of these lesions are investigated, and an etiologic hypothesis is presented to account for their clinical and pathologic associations.2

Patients and Methods

Two hundred and forty patients underwent technically satisfactory brain imaging at the MRI unit of Barrow Neurological Institute during six months of routine clinical operation. All patients were referred by a neurologist or a neurosurgeon, and 208 patients underwent a computed tomographic (CT) scan of the head as part of their evaluation. An additional 9 patients with a history of head trauma or craniotomy within the previous six weeks, and 43 patients with definite or probable demyelinating disease were evaluated during the same period but were excluded from the study. All patients completed a questionnaire addressing current and past medical history. The referring physician was also asked to complete a brief questionnaire about the reasons for MRI scanning and the patient's current neurologic status. Information was supplemented or clarified by communication with the referring physician or review of the medical records.

Magnetic resonance imaging (MRI) was performed using a 1.5 Tesla superconductive unit manufactured by General Electric Corporation. Scanning was done in the orbitomeatal plane with sections 5 mm thick and a scanning time just under nine minutes. A multiple
Definition and Grading of Incidental MRI Lesions

The MRI scans were reviewed by two investigators blinded to the clinical data. Special attention was directed to focal parenchymal areas of increased signal intensity. These were noted and cataloged to location, size, and multiplicity. The clinical information and other radiologic studies were subsequently analyzed, and incidental MRI lesions were identified. Incidental lesions (ILs) were defined as parenchymal foci of increased signal intensity which could not be explained by the patient’s current clinical diagnosis, neurologic examination, or CT scan. The criteria for an IL are listed in table 1, and were strictly adhered to throughout this study. For example, in a patient with cerebellar and bilateral thalamic foci on MRI, a cerebellar infarct clinically and on CT scan, and no known thalamic pathology, only the thalamic lesions would be counted as ILs. Similarly, in a patient with an isolated MRI lesion in the right thalamus, a left hemi-hypoesthesia clinically, and a normal CT, no ILs would be counted.

The ILs were graded according to a scale illustrated in figure 2. MRI scans without ILs were designated grade 0. Scans with focal ILs confined to one lobe of the brain or the posterior fossa were designated grade 1. Scans with multiple ILs involving more than one lobe of the brain were designated grade 2. MRI scans with multiple confluent ILs forming large patches were designated grade 3. An MRI study which was borderline between two grades was automatically assigned the lower grade.

Clinical Correlations and Multivariable Regression Analysis

The prevalence and severity of ILs were correlated with age and sex in the whole sample (N = 240) using four age categories and four MRI categories (grades 0–3). For the purpose of risk factor analysis, elderly patients were defined as those over 50 years of age. This subsample (N = 82) was further divided into three age categories (51–60, 61–70, and over 70). The prevalence and severity of ILs in these three age categories were compared. Additional correlations were performed examining the effects of a previous history of cerebrovascular disease (prior TIAs, RINDs, or strokes), hypertension (systolic over 160 mm Hg or requiring pharmacologic therapy), diagnosed diabetes mellitus, symptomatic coronary artery disease, and overt dementia (formal diagnosis by the referring neurologist) on the prevalence and severity of ILs in the elderly subsample. Statistical analysis was performed using Chi-Square tests with Yate’s continuity correction. A P value was calculated for each comparison using the tail end analysis and standard statistical formulae.

A multivariable linear regression analysis was performed on the whole sample assessing the relative contribution of each factor to the presence and severity of ILs. The SPSS statistical software package (SPSS Inc., Chicago, Illinois) designed for the IBM-PC computer was used. The Stepwise/Text protocol designed for examining interdependent variables was applied, assigning a standardized score to each variable. An equation was derived predicting the grade of incidental MRI lesions (0–3) from age and other significant variables (including unknown factors).

Results

Correlation of Incidental MRI Lesions with Age and Sex

Ages ranged from 5 to 82 years, with all age groups well represented (mean age = 49.2; median age = 70.5).

Table 1 Criteria for an Incidental Lesion on Magnetic Resonance Imaging of the Brain

| Lesion has increased signal intensity on T2 weighted images, and is identified by two investigators. |
| Lesion cannot be directly explained by the patient’s current clinical diagnosis. |
| Lesion cannot be directly explained by the patient’s current neurological examination. |
| Lesion is not visualized on a good quality CT scan. |
FIGURE 2. Grading of incidental MRI lesions. Grade 0: no incidental lesions. Grade 1: focal incidental lesions limited to one lobe of the brain or the posterior fossa. Grade 2: multiple incidental lesions extending beyond one lobe of the brain or the posterior fossa. Grade 3: confluent incidental lesions forming multiple large patches.

46). Figure 3 illustrates the incidence and severity of ILs in various age groups. One or more ILs was identified in 22% of patients 0–20 years of age, 22% of patients 21–40 years of age, 51% of patients 41–60 years of age, and 92% of patients over 60 years of age. The frequency of diffuse and confluent ILs (grades 2 and 3) increased steadily with age. The age association was statistically significant (p < 0.0005), and was maintained within the male subsample (p < 0.01), the female subsample (p < 0.01), and the subsample of patients over 50 years of age (p < 0.05). While ILs were clearly more prevalent in females, this correlation was lost after correction for age (the female subsample was strongly biased with older patients).

Clinical Correlation of Incidental MRI Lesions
The clinical indications for MRI varied widely and were expectedly different in the various age groups. Among 106 patients less than 40 years of age, 9 focal ILs (grade 1) were identified. All nine were in epileptic patients and corresponded to a probable seizure focus in 4 cases. There were 12 cases of multiple nonconfluent ILs (grade 2). These occurred in the patients with neurofibromatosis (3 cases), previous brain tumor with radiation therapy (6 cases), and possible multiple sclerosis (3 cases). In this age group, there were 2 patients with confluent ILs (grade 3). Both were females in their 30s with possible multiple sclerosis.

Interestingly, none of 22 patients under 40 years of age with previous brain tumor and no radiation therapy had an IL. Also, none of 48 patients with headache and no other neurologic disease had an IL. Because of the relatively small number of patients with ILs under 40 years of age, and the myriad of clinical presentations, no statistically significant associations emerged.

Among 134 patients over 40 years of age, ILs occurred with increasing frequency and severity with advancing age (fig. 4). In this age group, ILs were identified among patients in every clinical setting, including patients with headache and patients with brain tumors without previous radiation therapy. With the exception of cerebrovascular disease, no definite relationship with any particular clinical presentation could be demonstrated.

Correlation of Incidental MRI Lesions with Risk Factors for Cerebrovascular Disease
Prior history of brain ischemia among patients over 50 years of age was associated with an increase in the incidence of ILs (p < 0.05). This increase was manifested almost exclusively by a shift to multiple bilateral confluent lesions (grade 3) (fig. 4). This increase was not an effect of age, since the two groups were matched for age.

Prior history of hypertension (as defined) was associated with a similar increase in the frequency of ILs (p < 0.05). However, this increase was manifested almost exclusively by a shift to multiple nonconfluent lesions (grade 2) (fig. 5). Again, this increase was not an effect of age.

Diabetes mellitus and coronary artery disease were both associated with trends toward more frequent ILs. These trends were not statistically significant, and disappeared after correction for hypertension and age respectively. The frequency of ILs among 14 elderly patients with the overt diagnosis of dementia was identical to that among 68 elderly patients without this diagnosis.

Finally, age was correlated with the incidence and severity of ILs in the 33 elderly patients without prior history of cerebrovascular disease, hypertension, diabetes mellitus, coronary artery disease, or dementia. There was a consistent trend toward more frequent and more severe ILs with advancing age among these oth-
MRI IN THE ELDERLY: I. CLINICAL CORRELATIONS/Awad et al

CORRELATION OF INCIDENTAL SUBCORTICAL MRI LESIONS WITH PREVIOUS HISTORY OF BRAIN ISCHEMIA IN 82 CONSECUTIVE PATIENTS OVER 50 YEARS OF AGE

FIGURE 4. Correlation of a prior history of ischemic cerebrovascular disease with incidental MRI lesions in patients over 50 years of age. Lesions which correspond clinically to previous infarcts, and lesions visualized on CT are not considered incidental.

Multivariable Regression Analysis of Incidental MRI Lesions in the Elderly

The relative contribution of age, dementia, and risk factors for cerebrovascular disease to the presence and severity of incidental MRI lesions was assessed (table 2). Age, previous history of brain ischemia, and hypertension significantly and independently correlated with the MRI grade ($p < 0.01$ in each instance). The standardized correlation coefficients were 0.5, 0.2, and 0.2 for these three variables respectively. Clearly, age was the strongest predictor of the MRI grade, but prior brain ischemia and hypertension both contributed to the process. The predicted grade of incidental MRI lesions (0–3) can be estimated from the following equation:

$$
MRI = 0.46 \text{(Age)} + 0.54 \text{(ISCH)} + 0.47 \text{(HTN)} - 1.4
$$

where MRI is the MRI score (0–3), AGE is the age in decades, ISCH is the presence or absence of prior brain ischemia (0 or 1), and HTN is the presence or absence of hypertension (0 or 1).

DISCUSSION

Patchy foci of increased signal intensity are often identified on MRI of the brain. While some of these lesions occur in conjunction with known or suspected multifocal neurologic disease, similar parenchymal changes are often unexpected or incidental. In some cases, these incidental findings undoubtedly reveal early or less severe forms of occult neurologic disease. In other cases, they represent previously unrecognized alterations in the brain in response to a known systemic or neurologic pathology. In yet other cases, such lesions may be benign markers of normal physiologic processes such as senescence.

The problem of subcortical MRI lesions in the elderly has been addressed in several preliminary reports. However, the populations studied, the scanning techniques, and the definition and grading of lesions were necessarily different from our own. Using a less powerful 0.35 Tesla unit, Bradley, et al. demonstrated patchy confluent white matter lesions (grade 3 by our classification) in 6 of 20 consecutive patients over the age of 60. While some of these lesions occur in conjunction with known or suspected multifocal neurologic disease, similar parenchymal changes are often unexpected or incidental. In some cases, these incidental findings undoubtedly reveal early or less severe forms of occult neurologic disease. In other cases, they represent previously unrecognized alterations in the brain in response to a known systemic or neurologic pathology. In yet other cases, such lesions may be benign markers of normal physiologic processes such as senescence.
A similar confluent foci on MRI. There was a high incidence of dementia, stroke, and hypertension among these patients. One autopsied case revealed large patches of demyelination surrounding multiple minute lacunar infarctions of various ages. Dougherty, et al. recently reported another 23 patients with similar MRI and CT characteristics. All had motor deficits, long tract signs, and cognitive deficits in conjunction with severe risk factors for cerebrovascular disease. Nine had frank pseudobulbar palsy. One case was autopsied and reportedly showed numerous white matter infarctions. The reports of Kinkel and Dougherty both suggest that patients with progressive subcortical ischemic encephalopathy (Binswanger's disease) exhibit confluent subcortical foci of increased signal intensity of MRI. These reports and others do not explain the incidence of multiple white matter lesions on MRI. 

Before embarking on a meaningful analysis of these ILs, we sought to define them precisely and to grade them according to an objective and reproducible scheme. While we suspected that the various grades probably represent an increasing severity of the same process, we did not overlook the possibility of more than one process contributing to these changes. As with all diagnostic techniques, we recognized that the imaging protocol, the equality of the scans, and the magnetic resonance system used may well contribute to the number and severity of visualized ILs.

Despite the above assumptions and limitations, interesting trends were uncovered. As implied by previous scattered reports, ILs were infrequent below the age of 40. In this age group, they often occurred in the setting of a seizure disorder, and may have represented otherwise occult lesions causing epilepsy (i.e. hamartomas, occult neoplasms, cortical sclerosis, etc). Alternatively, the lesions may have reflected changes in brain parenchyma resulting from long standing seizures. Both possibilities are intriguing and should be investigated further. MRI lesions were prevalent in another clinical setting in this age group: the previous operated and radiated tumor. In such cases, ILs may have represented subtle parenchymal changes resulting from radiation therapy to the brain. Undoubtedly, other patients with ILs may eventually prove to have demyelinating disease.

Incidental MRI lesions were common above the age of 40 and increased in frequency and severity with advancing age. They occurred in a wide variety of clinical settings. With the exception of cerebrovascular disease, no significant association with any particular clinical presentation was demonstrated. Age, a prior history of brain ischemia, and hypertension were the most significant predictors of the incidence and severity of ILs. Diabetes mellitus, heart disease, and unknown factors played a less important role. While this study was not designed to specifically address the effect of dementia, elderly patients with the overt diagnosis of dementia did not have more frequent or more severe ILs than age matched controls. Even though all cases were referred by a neurologist or neurosurgeon,

Table 2: Multivariable Linear Regression Analysis of Incidental MRI Lesions in 240 Consecutive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SEB</th>
<th>Beta</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.461</td>
<td>0.057</td>
<td>0.545</td>
<td>0.471</td>
<td>0.370</td>
</tr>
<tr>
<td>Sex</td>
<td>0.069</td>
<td>0.154</td>
<td>0.179</td>
<td>0.174</td>
<td>0.261</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.508*</td>
<td>0.026</td>
<td>0.222*</td>
<td>0.206*</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.7</td>
<td>0.714</td>
<td>0.003</td>
<td>2.70</td>
<td>0.142</td>
</tr>
<tr>
<td>Arterial disease</td>
<td>0.000</td>
<td>0.714</td>
<td>0.003</td>
<td>0.008</td>
<td>0.158</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.000</td>
<td>0.566</td>
<td>0.556</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

B: the partial regression correlation coefficient for each variable.
SEB: the standard error of B.
Beta: the partial regression correlation coefficient expressed in standardized Z score form.
T: the t value (measure of variance) partitioned to each variable.
p: the significance level for the correlation of each variable.
*: significant correlation at the 0.05 level.
many patients without overt dementia may have demonstrated subtle abnormalities on formal neuropsychological testing. This issue would best be resolved by a prospective study on normal elderly patients, including neuropsychological testing and control for cerebrovascular risk factors. Such a study is already in progress at this institution.

Much remains to be learned about the clinical significance of incidental MRI lesions. However, it is clear from these findings and from previous reports that subcortical MRI lesions in the elderly may reflect an index of chronic cerebrovascular disease. Occult subcortical infarctions are known to occur in the elderly,19,20 and can appear as foci of increased signal intensity on MRI.1, 3, 11 Extensive lacunar degenerations are seen in cases of Binswanger’s disease and may explain the MRI findings in that setting.2, 11 However, it seems unlikely that multiple infarctions can afflict large areas of subcortical white matter and nuclei without overt neurological symptoms. Changes within the brain parenchyma other than frank infarction must be postulated to explain the majority of incidental MRI lesions. Such changes must be more frequent with advancing age and more prevalent with risk factors for cerebrovascular disease.

The vulnerability of deep areas of the brain to ischemia has been discussed in several reports.1, 5, 6, 10, 11, 20 The periventricular regions can be viewed as watershed zones of circulation between cortical penetrating vessels and deep perforating vessels. Long-standing cerebrovascular disease, including arteriosclerosis and lipohyalinosis may result in chronic parenchymal alterations in these areas. Such “wear and tear” was recently proposed by Ewing, et al. to explain the chronic decrease in regional cerebral blood flow which accompanies aging and cerebrovascular risk factors.8

The precise histopathological correlates of such “wear and tear” remain to be elucidated. In part II of this report, we present a pathological study of subcortical MRI lesions in the elderly, and propose an etiological hypothesis which accounts for their clinical and pathological associations.2

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