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Foci of Increased T2 Signal Intensity on Brain MR Scans of Healthy Elderly Subjects

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Foci of increased T2 signal intensity were found on brain MR scans in 16 (59%) of 27 healthy elderly volunteer subjects, ages 63 to 86 years old. These foci were not related to cognitive function or cerebrovascular risk factors; instead, they were highly correlated to age, being present in 11 of 11 subjects aged 75 years and over.

Recently, white matter abnormalities have been recognized with T2-weighted MR imaging in a substantial number of elderly patients [1–7]. These areas are less commonly seen as foci of low X-ray attenuation, or hypodensities, on CT scans [3, 8–14]. Lesions have been identified both in the nondemented elderly [3, 7, 15–17] and in patients with Binswanger [16] and Alzheimer [18] diseases. Hachinski et al. [19] dubbed these white matter lesions “leuko-araiosis.” Previous studies have reported subjects who were referred for medical evaluation. The purpose of this study is to determine the presence and extent of increased T2 signal intensity lesions in a population of healthy elderly subjects collected for future prospective studies and to correlate these lesions with cognitive function, cerebrovascular risk factors, and neurologic examination.

Subjects and Methods

All subjects were elderly volunteers who responded to advertisements in the Indiana University staff newsletter or notices sent to local senior citizens’ centers. All subjects had at least 2 years of post-high school education. Most were college graduates. After informed consent was obtained, extensive neurologic and psychiatric evaluations were performed. The neuropsychiatric evaluation included the DeMyer Standard Interview and the CAMDEX, a reliable structured psychiatric interview designed to diagnose mental disorders in the elderly [20, 21]. In addition, the Digit Symbol Test of the Wechsler Adult Intelligence Scale (WAIS) was administered [22]. Interviews were conducted both with the subjects and their spouse or key informant. The neuropsychological subscale of the CAMDEX is the CAMCOG. This scale includes all of the items pertaining to the Mini Mental Status Examination (MMSE) [23]. The CAMCOG total possible score is 110. In previous studies with this instrument a score below 79/80 was indicative of a dementing disorder. The total possible score on the MMSE is 30. Scores below 24 are usually associated with a dementing disorder. Subjects were assessed for historical cerebrovascular risk factors including diabetes mellitus, brain ischemia (TIA or stroke) or hypertension, angina or myocardial infarction, smoking, and drinking. Neurologic findings that have been associated with dementia or white matter lesions were assessed [6, 8, 10, 12, 24]. These include Babinski signs; persistent blinking with glabellar tapping; pucker, snout, and suck reflexes; forced grasp; asymmetric motor examination or asymmetric muscle stretch reflexes (MSRs); gait abnormalities; and urinary incontinence.

As the purpose of this research was, in part, to collect a cohort of healthy elderly subjects for future longitudinal studies, anyone with significant current medical or neurologic illness was excluded from further investigations. Eight subjects were thus excluded. These included two with evidence of early dementia, one of whom had a stroke, two with mild hypertension despite treatment, one with symptoms of Parkinsonism, one with myasthenia taking predni-

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sone, one with symptoms suggestive of amyotrophic lateral sclerosis, and one subject with an isolated finding of an upturned plantar reflex. Four other subjects refused further imaging studies. A total of 27 normal subjects were included, comprising 10 men and 17 women with ages ranging from 63–86 years (mean, 72.4 years). No cognitive decline in these subjects was reported either by self-description or from information provided by key informants.

All subjects had MR scans on a Picker unit with a variable-strength (1.5 T) superconductive magnet. Both T1-weighted, 800/26 (TR/TE), and T2-weighted, 2000/90, sequences with a slice thickness of 10 mm were obtained. The presence, extent, and severity of increased T2 foci in subcortical brain areas were rated in a blinded fashion by two observers using a four-point scale described by Awad et al. [1]. Grade 0 scans had no foci of increased T2 signal; grade 1 scans showed foci confined to one lobe of the brain or to the posterior fossa; grade 2 consisted of multiple foci involving more than one lobe of the brain; and grade 3 scans revealed multiple confluent foci forming large patches (see Fig. 1). Good reliability was attained with this scale (Cohen Kappa 0.69). The final ratings used in this study represent a consensus of the opinions of the two raters.

Results

The results of the MR scan ratings are shown in Table 1. Sixteen of 27 subjects (59%) had foci of increased signal intensity on T2-weighted scans. Of these positive scans, two were grade 1, six were grade 2, and eight were grade 3. There were no significant differences between men and women and presence of increased T2 foci. Based on a one-way analysis of variance, there was a significant difference in age for the rating categories. The mean ages of the four categories (grades 0–3) were 67.5, 73, 77, and 76.9 years, respectively ($p < .0002$) (Table 1).

There were no significant differences in estimates of cognitive performance on the MMSE, the CAMCOG, and the WAIS Digit Symbol Test (see Table 1).

As might be anticipated from the deliberate selection of healthy subjects, few had a prior history of serious medical illness (Table 2). Two subjects had a history suggestive of

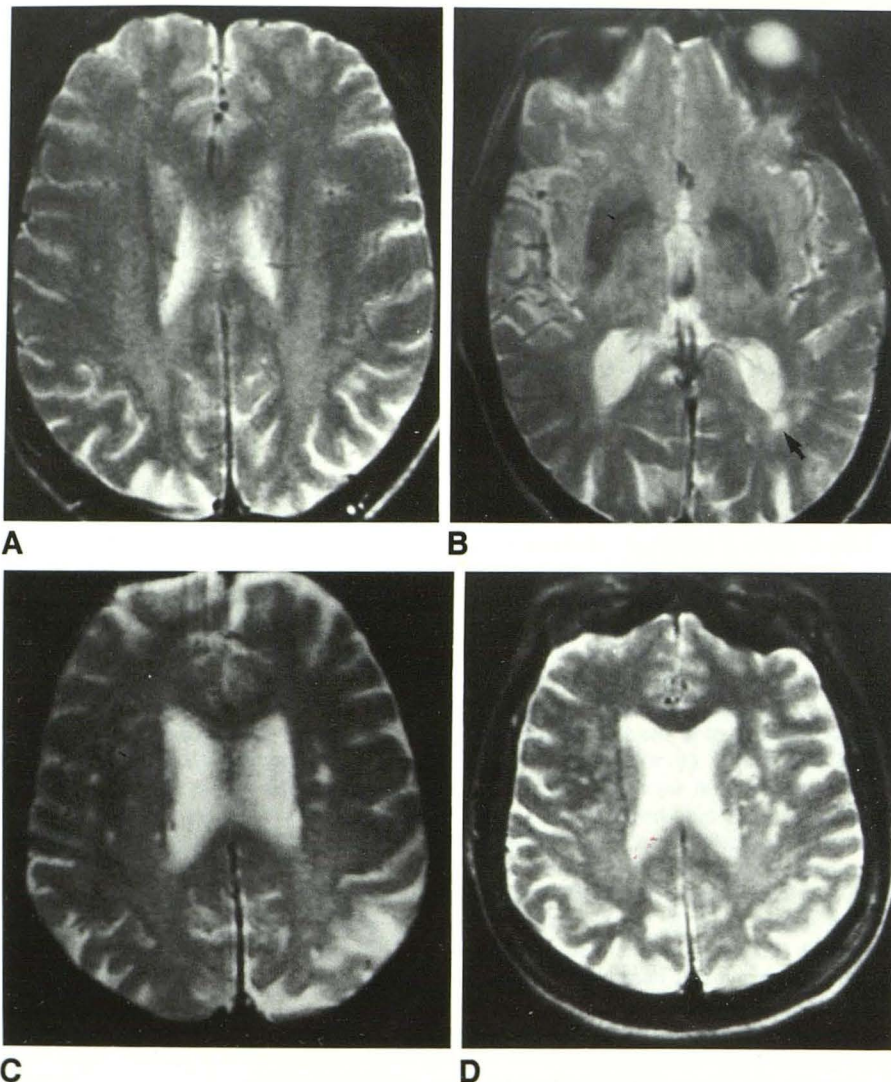


Fig. 1.—A, MR image with rating of grade 0—no foci of increased T2 signal: 73-year-old man with no gait abnormality and no history of cardiovascular risk factors.

B, MR image with rating of grade 1—foci confined to one lobe: 80-year-old woman with no gait abnormality and no history of cardiovascular risk factors.

C, MR image with rating of grade 2—multiple foci: 75-year-old man with no gait abnormality and no history of cardiovascular risk factors.

D, MR image with rating of grade 3—confluent foci forming large patches: 78-year-old woman with gait abnormality and no history of cardiovascular risk factors.

TABLE 1: Presence, Extent, and Severity of Increased T2 Signal Foci in Brains of Healthy Elderly Subjects Related to Mean Age and Cognitive Performance

Rating of Extent and Severity of T2 Signals ^a	No. of Subjects	Age ^b (SD)	MMSE Scores (SD)	CAMCOG Scores (SD)	Digit Symbol Raw Scores (SD) ^c
0	11	67.5 (±3.06)	28.5 (±1.81)	95.7 (±4.10)	41.4 (±8.35)
1	2	73.0 (±8.49)	29.0 (±0.00)	93.0 (±1.41)	46.5 (±21.9)
2	6	77.0 (±3.03)	29.0 (±1.26)	95.2 (±3.43)	38.8 (±10.6)
3	8	76.9 (±5.03)	28.8 (±0.89)	93.5 (±4.92)	41.8 (±4.97)

^a After Awad et al. [1].^b $p < .0002$.^c For grades 2 and 3 lesions, $n = 5$ in each group.**TABLE 2: Frequency (%) of Cerebrovascular Risk Factors According to MR Rating**

	Grade 0 ($n = 11$)	Grade 1 ($n = 2$)	Grade 2 ($n = 6$)	Grade 3 ($n = 8$)
Diabetes mellitus	9.1	0	16.7	12.5
Hypertension	27.3	0	33.3	25.0
Cardiac	0	0	16.7	12.5
Smoking	36.4	0	33.3	37.5
Heavy drinking	9.1	0	16.7	0

heart attacks. Their MR ratings were grade 2 and grade 3. Seven subjects reported previous treated hypertension. Of these, three had no T2 lesions, two had lesions of grade 2 severity, and two had grade 3 lesions. Three subjects reported a history of diet-controlled diabetes mellitus; one of these had no T2 lesions, one a rating of grade 2, and one a rating of grade 3. Nine participants reported being heavy smokers. Four of them had no white matter T2 foci, two had a grade 2 rating, and three had a grade 3 rating. Two subjects had a history of heavy drinking; one of these had no white matter changes and the other had a grade 2 lesion. None of these risk factors taken singly or in combination correlated significantly with the presence or severity of the MR lesions.

Nonfocal abnormalities on the neurologic examination, particularly frontal release signs, were common (Table 3). Nine of 27 subjects had a suck reflex, nine had a snout reflex, and five had a pucker reflex. Except for abnormal gait, abnormalities on the neurologic examination did not correlate with white matter lesions on MR. Gait abnormality was found in 0 of 13 subjects (0%) with grade 0 or grade 1 scans, but four of 14 individuals (29%) with grade 2 or grade 3 scans had difficulties (chi square = 4.04, $p < .05$). Of the four patients with abnormal gait, three had difficulty with tandem walking only, and one had a broad-based gait with diminished arm swing. Of the four subjects with gait abnormality, three had difficulty only with walking an eight-foot-long straight line, heel to toe. All these subjects lost their balance and moved their feet off the line to avoid falling. Gait in these individuals when their base was not narrowed was within normal limits.

TABLE 3: Frequency (%) of Abnormalities on Neurologic Examination According to MR Rating

	Grade 0 ($n = 11$)	Grade 1 ($n = 2$)	Grade 2 ($n = 6$)	Grade 3 ($n = 8$)
Abnormal gait*	0	0	14.3	37.5
Asymmetric power	0	0	0	0
Asymmetric reflexes	0	0	0	0
Forced grasp	0	0	0	0
Glabellar tap	18.2	0	14.3	0
Incontinence	0	0	0	0
Pucker	18.2	50.0	14.3	12.5
Snout	36.4	0	28.6	37.5
Suck	27.3	0	42.9	37.5

* $p = .044$ combining grades 0 and 1 and grades 2 and 3 for comparison.

Discussion

The frequency of increased T2 signal lesions in MR imaging in elderly patients in previous reports has varied from 30 to 93.5%, with most authors reporting more than 75% [1, 4, 6, 7, 15]. Our rate of 56.7% was somewhat lower. Rates of lesion detection are probably influenced by scanning parameters as well as study population selection factors. Many previous studies have used lower-strength magnets [4, 6, 7, 15], which may be less sensitive in imaging white matter abnormalities. However, these studies also generally have been retrospective and composed of patients referred for imaging as part of a medical evaluation, factors that may contribute to an increased presence of abnormalities. The prevalence of these white matter lesions may have been lower in our sample because our subjects were healthy volunteers. Cerebrovascular risk factors have also been associated with a higher frequency of increased T2 signal lesions [1, 4, 11, 12, 16, 25].

In a study of 240 patients referred for MR, Awad and his colleagues [1] correlated the presence of subcortical foci of increased signal intensity with brain ischemia and hypertension. In a retrospective study, Gerard and Weisberg [4] found that 78.5% of patients older than 50 years who had both a history of cerebrovascular risk factors and cerebrovascular symptoms had periventricular high signal intensity lesions,

while only 7.8% of those with no risk factors or symptoms had such lesions. Hershey et al. [5] and others [6, 10, 13], however, found no correlation of at least some cerebrovascular risk factors to white matter lesions seen on MR scans. Hershey et al. [5] found no significant differences between patients with vascular dementia and nondemented patients with respect to duration of risk factors for cerebrovascular disease or white matter lesion severity scores. Sarpel et al. [6] found that hypertension, diabetes mellitus, and TIA or stroke were not significant factors for periventricular lesions. In our study, cerebrovascular risk factors were not significantly correlated with the presence of increased T2 foci when considered either singly or in combination. The discrepancy between our study and some previous studies may be in the relative lack of severity of the risk factors in our healthy subjects; for example, 25% of our subjects had a history of hypertension, but all had been successfully treated. As in previous reports, smoking did not appear to be correlated with increased T2 foci in our study.

It has been suggested that subjects with periventricular white matter lesions on MR have an early and potentially reversible stage of ischemic white matter encephalopathy [1, 26]. In our study, however, even those subjects with extensive white matter lesions showed no evidence of cognitive decline either from interviews with subjects or key informants or from neuropsychological testing. It is possible that leuko-araiosis may not be severe enough to cause decline in cognitive skills when it first appears on MR scans in normal patients, but may be severe enough to do so by the time it appears on CT scans, as was demonstrated by Steingart et al. [13]. It may also be possible that more intricate neuropsychological tests than the tests employed in this study would reveal more subtle signs of cognitive decline. It should also be pointed out that because this study involved healthy elderly subjects, it cannot address the question of whether the presence, extent, or severity of white matter lesions is related to the cognitive decline associated with dementia.

Babinski signs, palmomental and root reflexes, abnormal limb power, and gait abnormalities have been associated with white matter lesions on CT scans [8, 10, 12], and Steingart et al. [12] have suggested that this relationship is causal. We, however, found no association of increased T2 signal foci with asymmetric motor examination or palmomental or root reflexes. The lack of correlation of these findings to lesions on MR in our study may once again reflect the ability of MR to show white matter changes before they are clinically significant. Our findings of primitive reflexes (pucker, snout, and suck) in approximately one-third of our normal subjects are consistent with findings from previous reports [27, 28]. We did find that gait abnormalities, in particular tandem difficulties, are associated with white matter lesions on MR, but they are significantly correlated only when grades 0 and 1 and grades 2 and 3 are combined for comparison. The sensitivity of tandem walking in revealing early signs of gait apraxia, when overt apraxia is not seen, may be responsible for this correlation with T2 signal foci on MR. The four who exhibited the gait abnormalities were among the oldest subjects in our study, being 86, 80, 80, and 76 years old, respectively. The

presence of gait abnormalities may be related therefore to musculoskeletal problems associated with advanced age rather than with the presence of white matter lesions.

The most prominent finding from our study is the highly significant correlation between advancing age and the presence and extent of foci on increased T2 signal image even in a population over the age of 63 years. Our results are even more striking if our subjects are divided into those 75 years old and over and those under 75 years old. One hundred percent (11 of 11) of the subjects 75 years old and over demonstrated these lesions as opposed to only 31% (five of 16) of the subjects under 75 years old. Although there are a few reports of subjects in their eighties with no evidence of white matter changes [29], our finding is consistent with most previous studies that have demonstrated a correlation between advancing age and T2 foci in populations in which a wider age range was studied.

In summary, in this study of healthy elderly subjects, the presence of increased foci of T2 high signal intensity was not correlated with cognitive performance or cerebrovascular risk factors. It was strongly correlated with age, however. In view of our results, the interpretation of the significance of white matter lesions in MR scans in subjects 75 years old or over should be made with caution.

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