Incidental Brain Lesions on Magnetic Resonance Imaging and Neurobehavioral Functions in the Apparently Healthy Elderly

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Background and Purpose: Controversies exist whether incidental neuroradiological brain lesions in the elderly are associated with depressed neuropsychological function. To address this important issue in a cross-sectional study, we related brain lesions on magnetic resonance imaging to a variety of cognitive and neurobehavioral function tests in an independent, normal elderly population.

Methods: We studied 73 independent asymptomatic elderly individuals (mean±SD age 70±6 years) to determine the relations between degree of brain atrophy, location and number of "lacunes," and grade of periventricular hyperintense lesions with a variety of cognitive and neurobehavioral function scores.

Results: We found that severity of neuroradiological changes increased while neuropsychological function scores declined with age. After adjustment for the effect of age, advanced periventricular hyperintensities, but not brain atrophy or patchy "lacunar" lesions, were associated with declines in all neuropsychological functions tested.

Conclusion: We conclude that incidental advanced periventricular diffuse or patchy white matter changes may play a role in the development of cognitive and neurobehavioral impairments in apparently normal elderly persons. (Stroke 1992;23:175-180)

With the advent of new technology such as computed tomography (CT) and nuclear magnetic resonance imaging (MRI), there is increasing evidence that "asymptomatic" intracranial morphological changes are fairly common in apparently normal elderly subjects.\(^1-3\) Brain MRI in particular was proven to be very sensitive for the detection of silent cerebrovascular lesions such as patchy subcortical lesions and diffuse periventricular hyperintense lesions (PVHs).\(^4\) Although the exact underlying pathological processes are still unknown,\(^5-7\) incidental MRI lesions were shown to be associated with various cerebrovascular risk factors such as old age, high blood pressure, and diabetes mellitus, suggesting a vascular etiology.\(^2,8-10\) On the other hand, controversies exist whether these "silent" neuroradiological lesions in the elderly are associated with depressed neuropsychological function.\(^11-13\) This question is particularly important since incidental silent cerebrovascular damage might account, at least partly, for the development of overt intellectual impairment in the elderly.\(^14\)

To address this important issue in a cross-sectional study, we related brain MRI lesions to a variety of cognitive and neurobehavioral function tests in an independent, normal elderly population. Brain MRI scans were analyzed for degree of brain atrophy, location and number of lacunar lesions, and grade of PVHs.

Subjects and Methods

The study population consisted of 73 elderly subjects (24 men and 49 women) aged 59–83 (mean±SD 70±6) years. All subjects were volunteers recruited from the community who maintained an active daily life and were free from psychiatric, neurological, cardiovascular (except high blood pressure), respiratory, endocrine (including diabetes mellitus), or other major diseases. Hypertension, defined as blood pressure of >160 mm Hg systolic or >90 mm Hg diastolic, was present in 34 subjects (47%). No subject was receiving any psychoactive or antihyperten-
sive medication at the time of the study. Informed consent was given by every participant.

On all 73 subjects MRI was carried out using a superconducting magnet with a main field strength of 0.5 T (G-50, Hitachi, Ibaragi, Japan). The brain was imaged in the axial plane in 10-mm-thick slices. $T_1$-weighted images were obtained using a short spin/echo pulse sequence with a repetition time of 600 msec and an echo time of 20 msec. Proton density and $T_2$-weighted images were obtained using a long spin/echo pulse sequence with a repetition time of 2,000 msec and an echo time of 60 and 120 msec, respectively. The matrix was $256 \times 256$ pixels. The images were evaluated for degree of brain atrophy, location and number of “lacunes,” and grade of PVHs. The index of brain atrophy was obtained as the ratio of the area of the ventricle to the area of the parenchyma (VPR) as measured with planimetry. The areas were measured at two different levels, that is, at the caudate nuclei (VPR-I) and at the lateral ventricles (VPR-II), according to the method of Brinkman et al. Lacunes were defined as areas ($<1$ cm$^2$) of low signal intensity on $T_1$-weighted images that were visible as hyperintense areas on $T_2$-weighted images. Hyperintense punctate lesions on $T_2$-weighted images were not counted as lacunes if they were not visible as low-intensity areas on $T_1$-weighted images as previously described. Proton density images were evaluated for the extent of patchy or diffuse PVHs. The lesions were classified into four grades as previously described. Grade I was defined as no white matter lesions except for small triangular foci surrounding the frontal horns; grade II was defined as caps in both anterior and posterior horns of the lateral ventricles or additional discrete patchy subcortical white matter lesions beside or above the lateral ventricles. More extensive punctate periventricular white matter lesions and their early confluent stages were classified as grade III. Marked areas of high signal intensity that reached confluence completely surrounding the lateral ventricles were defined as grade IV. Since only two subjects showed grade IV PVHs, these two subjects were included in grade III for analysis. One author, a neuroradiologist, interpreted all MRI scans blinded to the clinical status of the subject.

Neuropsychological function was assessed by a psychometric staff using a battery of interview instruments and special devices for performance-based appraisals. The Mini-Mental State Examination (MMS), modified for use in Japanese, and the Hasegawa Dementia Scale (HDS) were used to measure overall cognitive function. Both tests measure verbal orientation, memory, and constructional ability.

The visuospatial cognitive performance test (VCP), a kind of eye-tracking performance vigilance task, was administered to evaluate neurobehavioral function. Briefly, a computer displays 10 circles, each of which corresponds to one of 10 keys on the keyboard. At random intervals any one circle abruptly changes to a star for several seconds. If a subject can correctly tap the corresponding key in time, the duration of the star’s appearance (appearance time) becomes progressively shortened. If the tap is either delayed or wrong, the next appearance time of a star becomes one step longer. A test session consisted of 40 trials, and at the end of each session the consecutive data for performance efficiency are displayed on the computer. The accumulated shortening of each appearance time from the initial appearance time of 100 arbitrary units was regarded as the VCP score. This test measures attention, nonverbal visuospatial orientation, and cognitive performance reaction time. A higher score indicates better visuospatial cognitive performance.

Manual dexterity was assessed using a panel with combinations of 10 hooks and 10 big and eight small buttons. There were three discrete measurements of time recorded for each participant (10 “hook-on”s, 10 big “button-on-and-off”s, and eight small “button-on-and-off”s). The average time for one hook and one big or small button was summed to obtain a total manual dexterity time in seconds, defined as the button score. A high button score indicates poor manual dexterity.
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Statistical analysis was performed using Biomedical Data Processing statistical software (University of California, Los Angeles, Calif.). The correlations between age and each neurobehavioral function were analyzed with Pearson’s test. Analysis of variance (ANOVA) and Bonferroni’s test were used to compare groups defined by PVH grade. Two groups were compared by using Student’s t test. To control for the effects of aging on function score among PVH groups, each score was adjusted to that for a person aged 70 years based on the linear regression equation between the function score and age. To exclude the effect of age on the relations between function tests, the linear effect of age was removed using partial correlations. The level of significance was 0.05. Results are reported as mean±SD.

Results

The degree of brain atrophy on MRI (VPR-I and VPR-II) was significantly correlated with age (r=0.35 and 0.32, respectively; p<0.01 for both; Figure 1). The number of lacunes also increased with age (r=0.25, p<0.05; data not shown). Thirty-four subjects (47%) had at least one lacune, with an average of 1.5 lacunes per subject. Of the 113 lesions 14 (12%) were located in the brain stem, 61 (54%) in the basal ganglia, and 38 (34%) in the deep white matter. No lacune was found in the cerebral cortex. There were 13, 41, and 19 subjects in PVH grades I, II, and III, respectively. The age of persons in the grade III group was significantly higher than that in the grade I and grade II groups (74±6 versus 68±4 and 69±5 years, respectively; p<0.05). The difference in age between grades I and II was not significant.

Age-related depression of each cognitive and neurobehavioral function was also observed (Figure 2). The correlation coefficients of the relation between age and the button score (r=0.59) or VCP score (r=−0.39) were higher than those for the relation between age and score on the MMS (r=−0.27) or HDS (r=−0.24).

The brain atrophy indexes (VPR-I and VPR-II) were not correlated with the number of lacunes (by Pearson’s test) or with the PVH grade (by ANOVA). The number of lacunes and the PVH grade were correlated. There were 0.7±1.7, 1.0±2.2, and 3.6±4.5 lacunes per subject in the groups with PVH grades I, II, and III, respectively (p<0.05 by ANOVA).

There were significant differences in each cognitive and neurobehavioral function among the three PVH grade groups. These differences were still significant after adjustment for the effect of age (Figure 3). In each test, the subjects with grade III PVHs showed depressed neuropsychological function compared with the subjects with grade I or II PVHs. There were no significant differences in any test between grades I and II. Neither lacunes nor brain atrophy were significantly correlated with any neuropsychological function test after adjustment for the effect of age.

There were significant relations between scores on the MMS and HDS and between score on the VCP and the button score (Table 1). Significant, although weak, relations between score on the MMS, but not
HDS, and the VCP score or button score were also observed. Partial correlation analysis, however, showed that only the relations between the VCP score and the button score and between scores on the MMS and HDS were significant after adjustment for the effect of aging.

Discussion

The clinical significance of brain MRI lesions incidentally seen in apparently healthy elderly subjects has been a matter of intense debate. We found that with advancing age, the severity of MRI abnormalities increased while neuropsychological abilities declined, even within the healthy elderly population. We observed an age-independent association between advanced periventricular white matter lesions and depression of neuropsychological function, a relation that has not always been demonstrated by previous studies. Rao et al.12 found no association between focal white matter hyperintense spots, which they called "leukoaraiosis," and cognitive declines in middle-aged healthy volunteers. Hunt et al.13 graded MRI scans in healthy elderly volunteers for severity of patchy or diffuse white matter hyperintensities and reported that cognitive function regressed with the grade of white matter hyperintensities but that this correlation was not significant after adjustment for the effect of aging. In contrast, Steingart and coworkers11 examined a cohort of "normal" elderly volunteers with CT together with psychometric testing for dementia and extensive neurological examination; these researchers found significantly lower scores on cognitive function tests and a higher prevalence of abnormal neurological findings in subjects with leukoaraiosis than in those without it.

Reasons for discrepancies among these studies cannot be immediately discerned. The data may well be influenced by the selection of subjects, the definition of MRI changes, and the neuropsychological test batteries employed. We more comprehensively quantified MRI findings than previous studies in healthy elderly populations that included persons with mild to moderate hypertension. More recent reports suggest that elderly subjects with cerebrovascular risk factors show a positive correlation between degree of leukoaraiosis and speed of mental processing.20 Moreover, other studies have suggested that leukoaraiosis was correlated with cerebral hypoperfusion in normal volunteers21 and patients with vascular dementia22 or that leukoaraiosis was associated with small-vessel disease.23

Our data indicate that neither brain atrophy nor silent lacunes by themselves were linked to neuropsychological depression in apparently healthy elderly subjects. Brain atrophy is a common finding in patients with dementia, as well as in normal elderly subjects. Thus, this finding itself may be nonspecific. Regarding lacunes, these changes may not necessarily represent true small infarcts but may represent various pathological processes such as état crible, demyelinated lesions, and gliosis. Our study argues against a direct link between silent "lacunar" lesions

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**FIGURE 3.** Graphs of differences in score on Mini-Mental State Examination (MMS), Hasegawa Dementia Scale (HDS), and visuospatial cognitive performance test (VCP) and in button score (Button-S) among three grades of periventricular hyperintense lesions (PVH) after adjustment for effect of age. Large open circles and vertical bars represent mean ± SD. Probability values were obtained by analysis of variance (ANOVA): * and **, p < 0.05 and p < 0.01, respectively, by Bonferroni test.
on MRI and dementia. In fact, the lacunes on MRI scans seen in normal elderly subjects are much smaller than infarcts seen in patients with vascular dementia.24

On the other hand, advanced PVHs predicted poor neuropsychological function. Although PVHs may have a heterogeneous etiology, such lesions might be more closely related to "global" ischemia in the deep white matter (and thereby be associated with depressed performance) than isolated lacunar lesions in elderly subjects.16 It should be noted that advanced PVHs in apparently normal elderly persons are not necessarily linked to Binswanger's disease because lesions and the development of vascular dementia.

A prospective study is urgently needed to determine the relation between the current status of these silent lesions and the development of vascular dementia.

Of particular note is that our study design is similar to that of Hunt et al.13 One possible reason why they failed to show an age-independent correlation between intellectual function and PVHs may be the difference in age of the subjects. The mean age of their study population (78.2±4.6 years) was substantially higher than that of ours (70±6 years). Since age may have a predominant effect on neuropsychological function in normal subjects, other factors including brain MRI changes may become progressively less potent with advancing age.

In conclusion, neuroradiological changes on MRI such as brain atrophy, asymmetric lacunes, and PVHs are common findings in apparently normal elderly subjects. Advanced periventricular white matter hyperintensities, in particular, are associated with depressed cognitive and neurobehavioral functions. A prospective study is urgently needed to determine the relation between the current status of these silent lesions and the development of vascular dementia.

References


TABLE 1. Relations Among Four Neuropsychological Function Tests

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*tp<0.01 and 0.05, respectively, different from 0.

KEY WORDS • aged • cognition • magnetic resonance imaging
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