

Ischemic Basis for Deep White Matter Hyperintensities in Major Depression

A Neuropathological Study

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Background: White matter hyperintensities on magnetic resonance imaging are increased in major depression in the deep white matter, especially in frontal areas. These lesions have been hypothesized to be ischemic in origin, but there have been no previous neuropathological studies in depression. We investigated the neuropathological basis of these lesions in depression, hypothesizing that they would be more frequently ischemic in origin in depressed subjects.

Methods: We carried out in vitro magnetic resonance imaging on 3 slices of brain tissue (2 frontal, 1 occipital) from 20 elderly subjects who had a history of major depression and 20 elderly controls. The films were blindly rated, and sections were prepared for neuropathological analysis from the same slices and stained conventionally and by means of immunohistochemistry for microglia, macrophages, and astroglia. Lesions on the films were identified in the tissue, blindly described neuropathologically, and subsequently divided into ischemic and nonischemic lesions.

Results: All the deep white matter hyperintensities in the depressed group were found to be ischemic, compared with less than a third of those in the control group, a highly significant difference ($P < .001$). This difference was due to smaller punctate lesions (< 3 mm), which were predominantly ischemic in depressed subjects but not in control subjects. Larger lesions were usually ischemic in both groups. Compared with control subjects, ischemic lesions were significantly more likely to be in the dorsolateral prefrontal cortex compared with the anterior cingulate cortex ($P = .003$) and the occipital cortex ($P = .01$) in the depressed subjects.

Conclusions: Deep white matter hyperintensities are more frequently due to cerebral ischemia, and such ischemic lesions are more frequently located at the level of dorsolateral prefrontal cortex in depressed subjects. Our findings strongly support the "vascular depression" hypothesis of late-life depression.

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MAGNETIC resonance (MR) imaging studies examining elderly patients with depression have identified an increase in hyperintensities in the subcortical white and deep gray matter.^{1,2} White matter hyperintensities (WMHs) have been divided into 2 types: those adjacent to the ventricular system (periventricular hyperintensities [PVHs]) and those separate from the ventricles in the deep white matter (deep white matter hyperintensities [DWMHs]). In depression, the frequency of PVHs appears to be comparable with that in age-matched control subjects, but DWMHs are increased.^{1,2} Such lesions appear most strongly linked to depression when they involve frontal-subcortical circuits that reciprocally link prefrontal areas (the dorsolateral prefrontal cortex [DLPFC] and the anterior cingulate cortex [ACC]) to the basal ganglia.³

White matter hyperintensities have clinical importance, as they predict a poor response to treatment and increased relapse rate,⁴ but their cause in depression remains unclear. Studies have shown WMHs to be associated with increasing age,^{5,6} vascular risk factors, and cerebrovascular disease.^{5,6} The few published neuropathological studies of WMH, eg, those by Awad et al,⁷ Chimowitz et al,⁸ and Fazekas et al,⁹ have included only a small number of subjects, with a variety of diseases, and none included any subjects with depression. These found that DWMHs reflect a mixture of pathologic conditions, with smaller punctate lesions often corresponding to dilated perivascular spaces and larger lesions to patches of ischemic damage, but other causes have been reported, eg, congenital cysts and demyelination.^{7,9}

We have carried out a neuroimaging-neuropathological correlative study to examine the neuropathological basis of

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WMHs in depression. On the basis of the above findings, and wider evidence of cerebrovascular disease contributing to depression in the elderly,^{10,11} we tested 2 hypotheses: first, that ischemic DWMHs would occur more frequently in the depressed group than in the control group, and second, that ischemic DWMHs would be more frequent in the prefrontal white matter in depressed subjects than in control subjects.

SUBJECTS AND METHODS

SUBJECTS

Brain tissue from 40 elderly subjects (20 depressed and 20 control) was obtained from our Neuropathology Department Brain Tissue Bank. Postmortem permission for research had been given and ethical approval granted for the study. Depressed subjects had suffered at least 1 well-documented episode of *DSM-IV* major depression and had never fulfilled criteria for other *DSM-IV* psychiatric disorders.¹² They had been treated by experienced psychiatrists who had made the diagnosis of unipolar depression, and 19 of the 20 had been inpatients in Newcastle upon Tyne, England. All had received standard antidepressant treatment, with selective serotonin reuptake inhibitors or tricyclic antidepressants singly or often in combination with other agents, and 11 had received electroconvulsive therapy. Eleven had had their first depression before age 65 years, and the mean age at onset for the group was 64 years. Control subjects had also been hospital inpatients in Newcastle upon Tyne and were known to be capable of living an independent existence, and a review of their medical records showed no evidence that they had ever suffered any psychiatric disorder.

The case notes of all subjects were searched for information about vascular risk factors, and the cause of death and details have been published previously¹³; there were no group differences on any vascular risk factor, and the groups were very similar in their cause of death. All subjects received a full postmortem examination (except one whose body was taken by the undertakers after brain removal), and the cause of death and delay to postmortem examination were recorded. Brains were dissected in a standard manner, a full neuropathological examination was carried out and subjects excluded if they met neuropathological criteria for any known causes of dementia (eg, Alzheimer disease) or other neurological disease, or had evidence they died of hypoxia.

MR IMAGING AND RATING OF WMH

To locate WMHs for pathological analysis, we carried out postmortem MR imaging. To facilitate translation from WMHs seen on MR imaging to the corresponding lesions in the tissue, we carried out *in vitro* imaging on coronal slices (7 mm thick) of formalin-fixed brain tissue. Previous studies have used *in vitro* scanning of such brain tissue and found the method to be valid.⁷ We designed a special apparatus made up of a number of plastic trays slotting on top of each other and shaped to fit into the knee coil of the scanner and piloted this with coronal slices to obtain the optimal imaging sequences.¹⁴ One of the depressed subjects with a large number of WMHs had had *in vivo* imaging about a year before he died and, comparing the *in vitro* images with this earlier image, we found all WMHs were clearly visualized on the slice images.¹⁴

Three coronal slices (right hemisphere) were scanned from each subject. We chose 2 slices from the frontal areas (DLPFC and ACC) that have been demonstrated to be abnormal in functional imaging studies^{15,16} and that include the frontal-subcortical circuits,³ and one from the occipital lobe as a con-

trol area to allow comparison with the prefrontal levels. Slices were removed from formalin, placed in sealed bags, laid out on trays, and taken immediately to the MR imager before any tissue degradation could occur. The MR imaging was performed on a 1.0-T imager (Siemens Magnetom Impact Expert; Siemens AG, Erlangen, Germany), and coronal 3-mm slices were acquired through each postmortem slice. Proton density and T2-weighted images were obtained with a dual spin-echo sequence (repetition time, 2500 milliseconds; echo time, 16/98 milliseconds), and a T1-weighted sequence was also obtained (repetition time, 6838 milliseconds; echo time, 60 milliseconds). The resulting films were coded so that rating was blind to diagnosis. Two experienced raters (J.T.O.B. and R.B.) used the rating scale of Scheltens et al¹⁷ to score the WMHs in all 120 slices.

NEUROPATHOLOGICAL ASSESSMENT OF WMH

After scanning, the tissue was embedded in paraffin and 10- μ m and 20- μ m sections were prepared on large slides (7.6 \times 5.1 cm) that were coded to enable the analysis to be carried out blind to diagnosis. Sections were stained with hematoxylin-eosin, Luxol fast blue, and cresyl fast violet. The hematoxylin-eosin enabled assessment of the integrity of the parenchyma and the microvasculature, Luxol fast blue indicated areas of myelin pallor, and cresyl fast violet was used to assess adjacent cortical tissue for evidence of microinfarcts or other abnormalities.

We also carried out immunocytochemistry for specific antibody markers of microglia (HLA-DR; 1:500; Dako Ltd, Cambridgeshire, England), macrophages (CD-68; 1:50; Dako Ltd), and astrocytes (glial fibrillary acid protein [GFAP]; 1:4000; Dako Ltd). HLA-DR is a major histocompatibility complex class II marker of microglia that is constitutively expressed but markedly increased when microglia are activated.¹⁸ Microglia are recognized to be exquisitely sensitive to perturbation of the central nervous system microenvironment,¹⁹ and ischemia is a potent stimulator of microglia.²⁰ CD-68 is an intracytoplasmic protein of macrophages, as well as microglia, and its expression is markedly increased by cellular activation, such as that following ischemia.^{18,21} Glial fibrillary acid protein is a marker of astrocytes, which are activated by ischemia but more slowly than microglia. They are central to the gliotic response to neuronal damage, and the extent of GFAP increase correlates well with the extent of neuronal damage.^{20,22}

Sections were processed for immunocytochemistry in a standard manner with the use of microwave antigen retrieval for HLA-DR and GFAP and protease retrieval for CD-68. After incubation with the primary antibody, appropriate secondary antibodies were applied, followed by avidin-biotinylated horseradish peroxidase complex (Vector Laboratories Ltd, Peterborough, England) and diaminobenzidine as a chromagen. The sections were repeatedly washed in Tris-buffered saline (pH, 7.6) between each stage in this process and finally lightly counterstained with hematoxylin.

Neuropathological assessment of the WMHs was carried out blind to diagnosis and patient identity by 2 experienced raters (A.J.T. and R.H.P.), who located the WMHs seen on the MR image in the corresponding sections from the tissue. This involved identifying the WMHs on the images, holding the slides beside the image on the light box, and marking the corresponding lesions on the slides (**Figure 1**). The raters then examined each lesion in turn by using each of the above 6 stains, described its neuropathological features, and paid careful attention to the presence or absence of evidence of ischemic tissue damage. A lesion was rated as ischemic if both raters agreed there was clear evidence of increased macrophage or microglial activity in the lesion and/or if there was evidence from GFAP of astrogliosis. In such lesions, inspection of the tissue by means of hematoxylin-eosin and Luxol fast blue stains showed loss

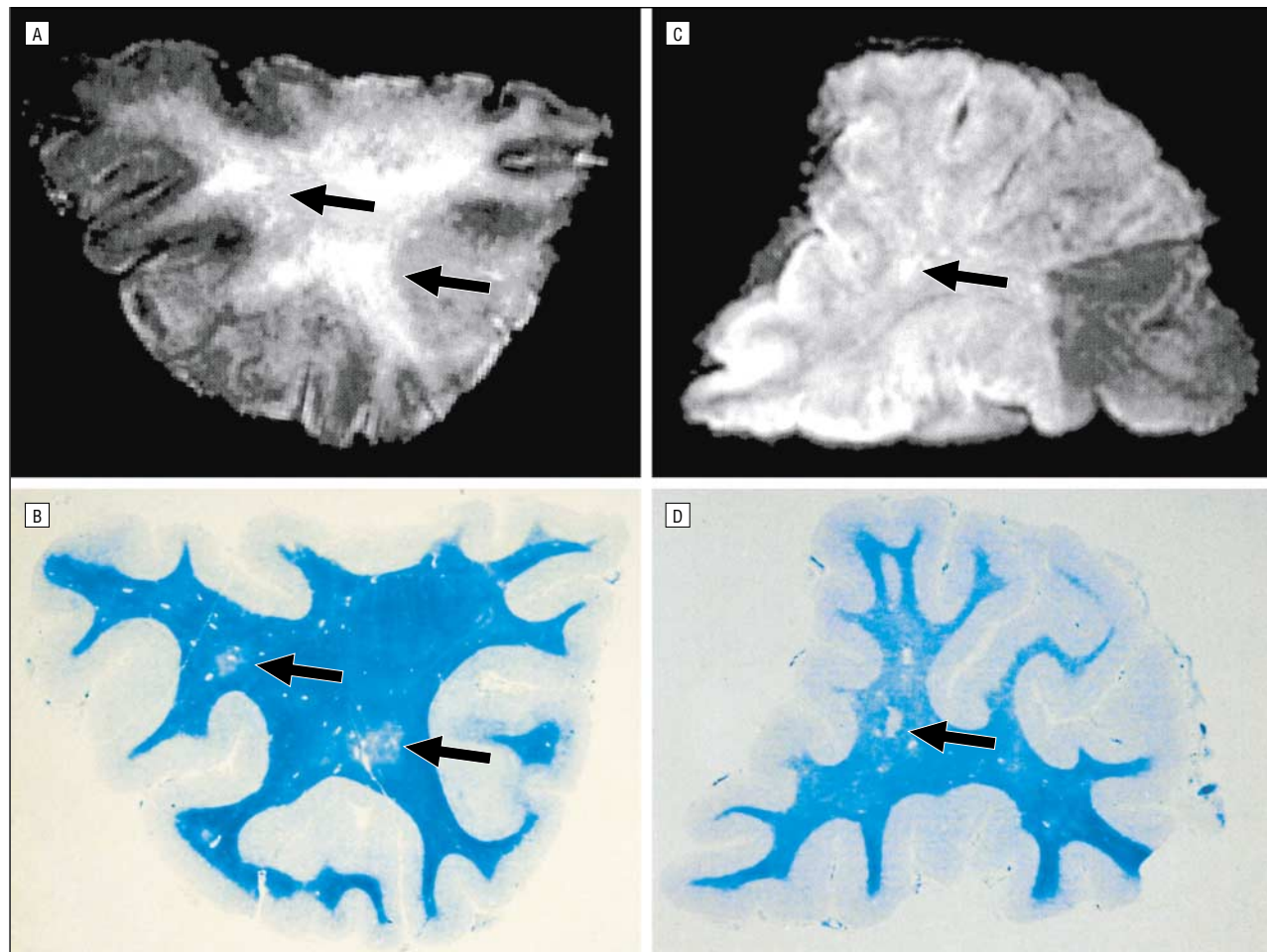


Figure 1. Deep white matter hyperintensities on in vitro magnetic resonance images and myelin-stained tissue. A, Arrows indicate 2 large deep white matter hyperintensities on a T2 sequence from the anterior cingulate cortex (there is also a periventricular hyperintensity not indicated by arrow). B, Same lesions in a Luxol fast blue-stained section from the same tissue. C, Arrow indicates a punctate deep white matter hyperintensity on a T2 sequence from the dorsolateral prefrontal cortex. D, Same lesion in the Luxol fast blue-stained section.

of myelin, thinning, and loss of fibers and cells. In a couple of cases where immediate agreement was not obtained, the slides were reviewed and discussed; the raters agreed that, since ischemia was not clearly present, such lesions should be classified as nonischemic. The histologic features of the white and gray matter tissue surrounding each lesion that had normal signal on MR imaging were also carefully examined to compare them with those of the tissue in the lesion.

To test the hypotheses, the planned analyses were to compare ischemic and nonischemic lesions in each group as a proportion of lesions examined pathologically by means of Fisher exact test to compare the lesions and their location in the two groups (SPSS version 10 software; SPSS Inc, Chicago, Ill). In addition, on the basis of previous findings,^{7,9} we also divided DWMHs according to their Scheltens et al rating¹⁷ into punctate lesions (score of 1 or 2, <3 mm) and larger lesions (score of 3-6, >3 mm), and unpaired *t* tests were used to compare groups on age and postmortem interval.

RESULTS

There were 7 men and 13 women in each group, and there were no significant differences in age (mean [SD], 75.0 [7.37] years in the depressed group and 74.2 [7.46] years in the control group; $t_{38}=0.30$, $P=.77$) or postmortem delay (mean [SD], 34.5 [22.7] hours in the depressed group

and 28.0 [16.2] hours in the control group; $t_{38}=1.05$, $P=.30$) between the groups. On the MR images, 38 DWMHs (19 in DLPFC, 17 in ACC, and 2 in occipital cortex) were rated in 13 subjects in the depressed group and 36 (17 in DLPFC, 16 in ACC, and 3 in occipital cortex) in 13 subjects in the control group; neither the total numbers nor the distributions were significantly different. In addition, 4 infarcts (2 in depressed subjects and 2 in controls) were identified and confirmed at pathological analysis. Thirty DWMHs seen on the images (22 in depressed subjects and 8 in control subjects) could not be identified on the slides taken from the slices. Most (26) of these were punctate lesions. On retrospective analysis, these missed lesions did not appear any different on the MR images from the lesions we were able to examine microscopically, nor did ischemic lesions appear different from nonischemic lesions on the images. This left 44 DWMHs (16 in 7 depressed subjects and 28 in 11 control subjects) that were examined microscopically and on which group comparisons are based.

These 44 DWMHs consisted of 30 punctate lesions and 14 larger DWMHs. Figure 1 shows examples of punctate and larger DWMHs from the in vitro MR images and the corresponding lesions in the tissue, and **Table 1**

Table 1. Frequency of Ischemic and Nonischemic Deep White Matter Hyperintensities in 7 Depressed and 11 Control Subjects*

	No. (%)		Fisher Exact Test, P Value
	Depressed	Control	
Ischemic DWMHs	16 (100)	8 (29)]. <.001
Nonischemic DWMHs	0	20 (71)	
Ischemic punctate DWMHs	9 (100)	3 (14)]. <.001
Nonischemic punctate DWMHs	0	18 (86)	
Ischemic large DWMHs	7 (100)	5 (71)]. .46
Nonischemic large DWMHs	0	2 (29)	

*Lesions were located in coronal slices of tissue (see "Subjects and Methods" section for details). DWMHs indicates deep white matter hyperintensities.

shows the ischemic and nonischemic basis of all 44 DWMHs. There was a highly significant increase in the proportion of ischemic DWMHs in the depressed group (Fisher exact test, $P < .001$). **Table 2** shows the number of subjects in each group who had any ischemic DWMHs compared with those who had none. There was also a significant increase in the proportion of depressed subjects with ischemic DWMHs (Fisher exact test, $P = .01$). To investigate whether these group differences were due to a disproportionately large number of ischemic DWMHs in 1 or 2 subjects, which might have confounded the results, we compared the frequency of lesions per subject in the 2 groups. The 16 ischemic DWMHs in the depressed group were found in 7 subjects (mean per subject, 2.29; range, 1-4), while the 8 ischemic DWMHs in the control group were found in 4 subjects (mean, 2.00; range, 1-4). There was no statistically significant difference in the frequency of ischemic DWMHs per subject between the 2 groups (Mann-Whitney test, $U = 11.5$; $P = .62$).

PUNCTATE DWMH

Table 1 shows the basis of the punctate DWMHs in each group and compares the proportions of ischemic and nonischemic lesions. Of the 30 punctate lesions analyzed microscopically, 21 were in control subjects. Thirteen were found to be dilated perivascular spaces with no evidence of any ischemia in the surrounding tissue (**Figures 2A and B**); 4 lesions corresponded to small foci of demyelination with no evidence of ischemia (**Figures 3C and D**); 3 lesions were dilated perivascular spaces with evidence of ischemic tissue damage in adjacent tissue (Figure 2C and D); and the other lesion corresponded to an abnormal conglomeration of small vessels. In the depressed subjects, 8 of the 9 punctate lesions were caused by dilation of the perivascular spaces with evidence of associated ischemic tissue damage (Figure 2C and D), and the other lesion was a small focus of demyelination that showed clear evidence of ischemic tissue damage (Figures 3E and F). Thus, all 9 punctate lesions in depressed subjects were associated with ischemia, while only 3 of the 21 punctate lesions in the control subjects showed evidence of ischemia. This difference was highly significant (Fisher exact test, $P < .001$). Table 2

Table 2. Numbers of Subjects With Ischemic and Nonischemic Deep White Matter Hyperintensities in Depressed and Control Subjects*

	No. (%)		Fisher Exact Test, P Value
	Depressed	Control	
Ischemic DWMHs	7 (100)	4 (36)]. .01
Nonischemic DWMHs	0	7 (64)	
Ischemic punctate DWMHs	4 (100)	2 (25)]. .03
Nonischemic punctate DWMHs	0	6 (75)	

*Lesions were located in coronal slices of tissue (see "Subjects and Methods" section for details). Subjects were classified as ischemic if they had any ischemic deep white matter hyperintensities (DWMHs) and nonischemic if they had none.

compares the groups by the number of subjects who had any ischemic punctate DWMHs compared with those who had none, and there was a significant increase in the proportion of depressed subjects with ischemic punctate DWMHs (Fisher exact test, $P = .03$).

LARGER DWMH

Table 1 shows the findings for larger DWMHs and compares the proportions of ischemic and nonischemic lesions. Of the 14 larger lesions, 12 corresponded to areas of demyelination associated with evidence of ischemia. These lesions showed oligodendrocyte loss and evidence of macrophage or microglial infiltration and/or the GFAP showed astrocytosis (as in Figures 3E and F, but these were larger lesions). CD-68 was found to be a more reliable marker for microglia than HLA-DR. Seven of these were in depressed subjects (5 with a Scheltens et al score of 3 [4-10 mm]; 2 with a score of 5 [>11 mm]) and 5 were in controls (4 with a score of 3; 1 with a score of 6 [confluent]). The 2 other larger DWMHs in the control subjects were lesions with scores of 5 and 6 that corresponded to areas of demyelination with some evidence of tissue thinning but no clear evidence of ischemia (no macrophage infiltration or astrocytosis; like Figures 3C and D, but larger lesions). Thus, for these larger lesions, all 7 in depressed subjects were due to ischemic tissue damage, while 5 of the 7 control subjects showed evidence of ischemia (Fisher exact test, $P = .46$).

DISTRIBUTION OF DWMH

Table 3 shows the distribution of the DWMHs. All 16 ischemic DWMHs in the depressed subjects were frontal (12 DLPFC and 4 ACC), while in the control subjects, only 6 ischemic DWMHs were frontal (all ACC) and the other 2 ischemic lesions were in the occipital lobe. Comparisons with control subjects showed a highly statistically significant elevation of ischemic DWMHs in the depressed group in the DLPFC compared with both the ACC (Fisher exact test, $P = .003$) and the occipital cortex (Fisher exact test, $P = .01$), but no significant difference in the ACC compared with the occipital cortex (Fisher exact test, $P = .42$).

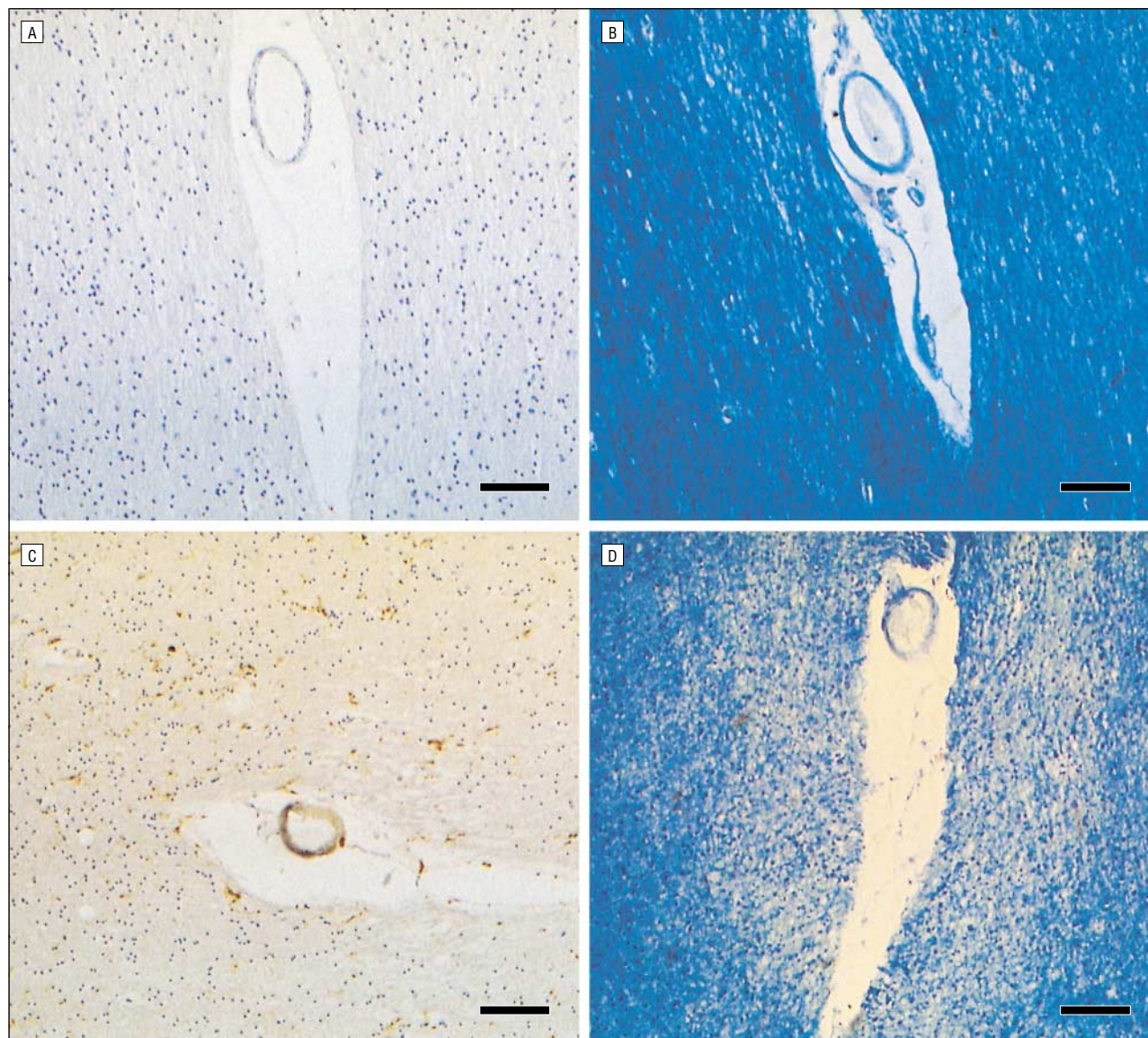


Figure 2. Dilated perivascular spaces with and without ischemia seen as punctate deep white matter hyperintensities on magnetic resonance images. A and B, Dilated perivascular space. There is no evidence of ischemia. C and D, Some pallor of the myelin (D) associated with microglial activity (C) indicating perivascular ischemia (HLA-DR with hematoxylin counterstain [A and C] and Luxol fast blue [B and D]; bars indicate 100 μ m).

COMMENT

This is the first study, to our knowledge, to examine the pathological basis of WMHs in depression. We found that all DWMHs examined in our depressed subjects showed evidence of ischemic damage compared with less than a third of these lesions in control subjects, a highly significant difference. While most larger lesions in both groups were ischemic, smaller punctate lesions were ischemic in depressed subjects but usually not in control subjects. It is important to note that ischemic DWMHs showed a marked specificity for the white matter at the level of the DLPFC in depressed subjects. Our findings strongly support the “vascular depression” hypothesis, which proposes that vascular disease predisposes to, precipitates, or perpetuates depression.

The high frequency of ischemic lesions in depressed subjects contrasted with their surprisingly low frequency

in control subjects. This was not due to an excess of vascular disease in the control subjects, as, paradoxically, they had more clinical vascular disease.¹³ Perhaps the most likely explanation is that DWMHs progress from nonischemic lesions to ischemic lesions when a certain threshold for ischemic damage is crossed. Thus, with normal aging, a mild loss of perfusion or age-related degenerative changes might induce loss of myelin without producing sufficient cell damage to activate microglia and macrophages. If there is a further reduction in perfusion, then immune cells and glia would be activated as ischemic damage develops and the DWMHs progress to ischemic lesions. It may be that such a threshold for progressing from nonischemic to ischemic lesions is lower in depressed subjects, making them more vulnerable to ischemia. Alternatively, depressed subjects may have a generally poorer perfusion of cerebral, especially prefrontal, tissue through some combination of large vessel, small vessel, and hypotensive disease pro-

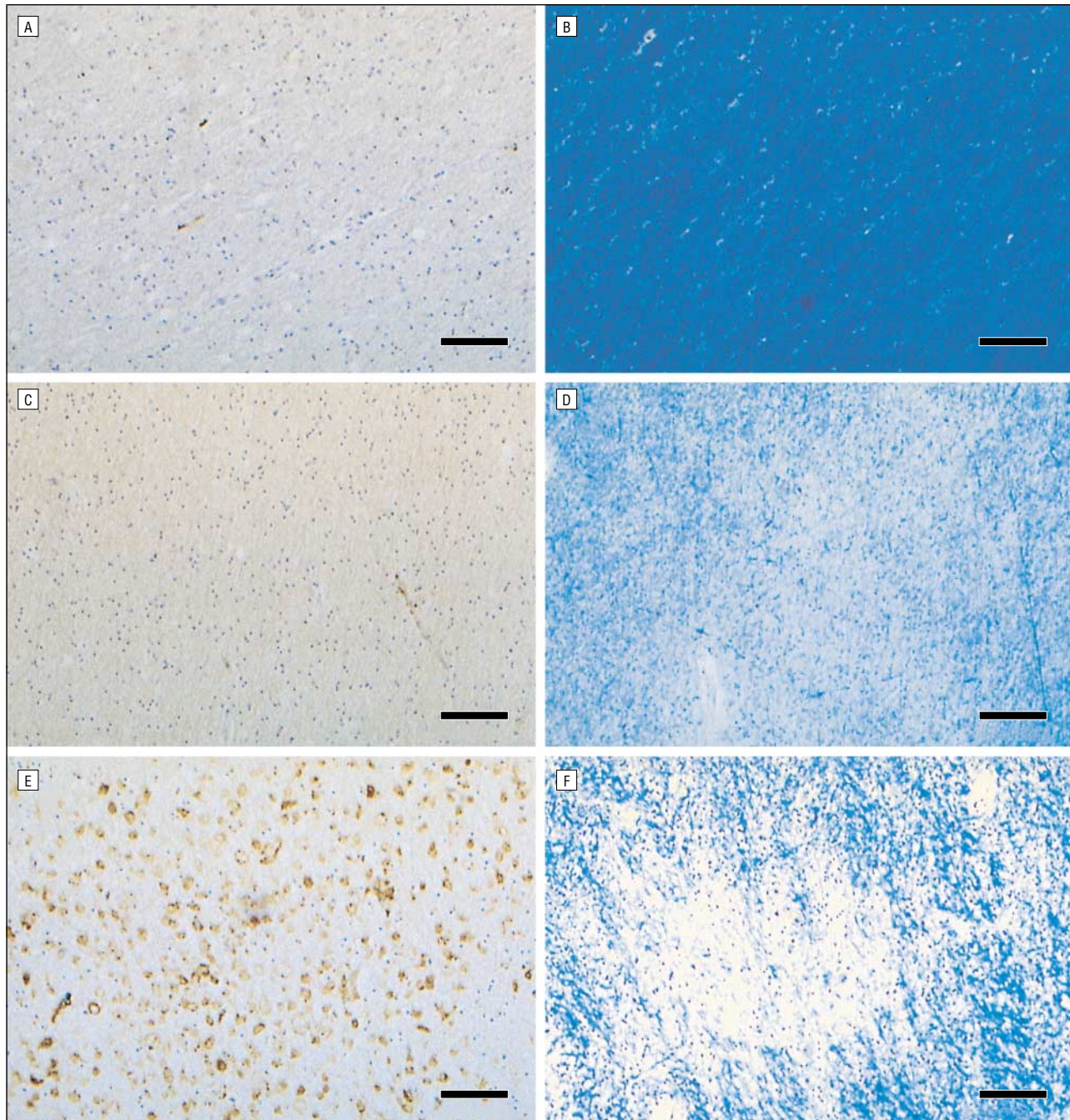


Figure 3. Deep white matter hyperintensities due to ischemic and nonischemic demyelination. A and B, Normal tissue for comparison. C, Normal HLA-DR staining. D, Myelin pallor. E and F, Phagocytic microglial infiltration indicating ischemic tissue damage (E) associated with marked pallor (F) (HLA-DR with hematoxylin counterstain [A, C, and E] and Luxol fast blue [B, D, and F]; bars indicate 100 μ m).

cesses. This alternative would harmonize with clinical studies, which have shown that depression is more common after myocardial infarction, stroke, and hypertension³ and that depression is also an independent risk factor for each of these conditions.²³⁻²⁵ The large difference between the groups in ischemic DWMHs was due to group differences in the frequency of punctate DWMHs. Cerebral ischemia associated with these lesions would appear to be important, and, although some have questioned the significance of punctate lesions²⁶ in general, Lenze and colleagues²⁷ found punctate lesions to be increased in late-life depression after controlling for vascular disease and

Simpson and colleagues²⁸ found punctate DWMHs to be the most robust predictor of poor clinical outcome in depression in the elderly. Our finding that punctate lesions are usually ischemic in depression therefore appears to be of clinical importance. The difference in the frequency of ischemic DWMHs between the groups was not due to 1 or 2 depressed subjects having a large number of ischemic lesions, because there were no differences in the frequency of ischemic DWMHs per subject between the groups and, more important, the difference therefore remained even when groups were compared by subjects rather than by lesions.

Table 3. Anatomic Distribution of the 44 Ischemic and Nonischemic Deep White Matter Hyperintensities*

	Depressed, No.	Control, No.
Ischemic DWMHs		
Dorsolateral prefrontal cortex	12	0
Anterior cingulate cortex	4	6
Occipital cortex	0	2
Nonischemic DWMHs		
Dorsolateral prefrontal cortex	0	15
Anterior cingulate cortex	0	4
Occipital cortex	0	1

*Lesions were located in coronal slices of tissue from each cortical level from 20 subjects per group (see "Subjects and Methods" section for details). DWMHs indicates deep white matter hyperintensities.

There was a striking difference in the distribution of ischemic DWMHs in the 2 groups. All the ischemic DWMHs were located frontally in the depressed group, and this was especially the case for the DLPFC, which had significantly more ischemic DWMHs than either of the other 2 areas. These findings imply that the burden of ischemia due to DWMHs is underestimated by MR imaging comparisons of depressed and control subjects, even though these comparisons show that DWMHs are more common in the frontal lobes.²⁹ Such lesions may contribute to the pattern of depression in the elderly and have clinical importance, because previous studies have demonstrated that executive dysfunction in depression in the elderly, associated with the DLPFC, predicts poor response to antidepressant treatment³⁰ and a higher frequency of relapses and recurrences.³¹

It is difficult to compare our findings with previous work, as no other study has examined WMHs in depression and the few published of WMHs in other conditions have not used specific markers for macrophages and microglia. However, the findings in the few published studies⁷⁻⁹ appear similar to ours in that punctate lesions were usually caused by dilated perivascular spaces, often with evidence of associated perivascular myelin pallor or gliosis, and larger DWMHs showed myelin pallor with or without gliosis. Earlier studies, eg, that of Awad and colleagues,⁷ also missed some lesions in the tissue, and this raises the question as to whether the missed lesions might be different from those examined microscopically. Review of the films after pathological analysis did not show the missed lesions to be any different, and, although it is likely that some DWMHs in depressed subjects are nonischemic, it is difficult to think of a reason why the DWMHs we examined should be systematically different pathologically from those we missed.

Our findings apply to severe depression, and the extent to which they can be generalized to late-life depression in general is unclear. However, although the early MR imaging studies in depression were carried out on similar clinical samples of subjects with severe depression, 2 recent large epidemiologic MR imaging studies of community depression have shown that DWMHs are increased in such depressed subjects too.^{32,33} This suggests that our findings may have a wider relevance to de-

pression in the elderly, not just to severe illness seen by specialists but also to milder community forms of depression. Since our results do not appear to be due to an excess of vascular disease in the depressed group, they imply, as has been suggested previously,^{3,11} that depression may be more closely linked to vascular disease than clinical risk factors show and may itself be regarded in the elderly as suggesting underlying cerebral ischemic processes. Certainly, our results demonstrate that WMHs should be regarded as evidence of cerebrovascular disease in elderly depressed subjects.

Our results strongly support the vascular depression hypothesis of depression, demonstrating that the majority of DWMHs in elderly subjects with severe depression are probably due to ischemia, and this is especially the case when they are located at the level of the DLPFC. Thus, not only are DWMHs more common in depression,^{1,2} but we have now shown that they are also much more likely to be due to ischemia in the cerebral white matter. The suggestion that depression in the elderly be viewed "as a potentially treatable variant of cerebrovascular disease"¹¹ and treated accordingly is supported by our study.

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