MRI-Defined Vascular Depression

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Objective: *The authors' goal was to characterize the clinical and demographic features of vascular depression.* *Method:* *They classified 89 depressed patients into two groups—those with vascular (N=32) and nonvascular (N=57) depression—on the basis of examination of brain magnetic resonance images. All of the patients were enrolled in the National Institute of Mental Health Clinical Research Center for the Study of Depression in Later Life, located at Duke University. The patients with vascular and nonvascular depression were compared on several clinical and demographic risk factors.* *Results:* *Bivariate analyses and a fully adjusted logistic regression model revealed that older age, late age at onset, and nonpsychotic subtype occurred more often in patients with vascular depression than in those with nonvascular depression. A family history of mental illness was found somewhat less often, and anhedonia and functional disability were seen somewhat more often in patients with vascular depression.* *Conclusions:* *The profile of patients with vascular depression needs to be developed further. This is likely to have important therapeutic and theoretical implications for the management of these patients.*

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Risk factors for the onset of depression in late life are poorly understood. Genetic factors appear to be less important in late-onset depression than in early-onset depression (1). In contrast, structural changes in the brain, especially vascular or ischemic changes, appear to be of more importance (2, 3). Fujikawa et al. (4) used the term "silent cerebral infarction" to describe the pathology in these patients. We had introduced the term "arteriosclerotic depression" to denote depression in patients with cerebrovascular or ischemic changes in the brain (5). The term "vascular depression" may be more consistent with the current conceptualization of vascular dementia in, for example, DSM-IV, where the multiple cognitive deficits are judged to be related to multiple infarcts in the brain. We conceptualize vascular depression as depression related to multiple infarcts in the brain (we discussed this with George S. Alexopoulos, M.D., of Cornell University Medical College).

In this paper we used data from the National Institute of Mental Health (NIMH) Clinical Research Center for the Study of Depression in Later Life, located at Duke University, to further advance our understanding of vascular depression. Using brain magnetic resonance imaging (MRI), we identified depressed patients with vascular changes and compared them with depressed patients without vascular changes. The classification was based on a patients' scores on a modified Fazekas scale (6) (described in the Method section). Because depressive symptoms can occur quite often in the early stages of vascular dementia, we excluded patients whose mental status was compromised to safeguard against the confounding effect of cognitive impairment.

Five hypotheses were tested: patients with vascular depression would 1) be older, 2) have a later age at onset, 3) have less family history of mental illness, 4) report more apathy (based on our previous study noting greater loss of interest among patients with late-onset depression [7]), and 5) have more functional impairment than depressed patients without vascular changes.

METHOD

Subjects and Design

The study used a case-comparison group design. Clinical and phenomenological data for this study were obtained from patients treated at the NIMH Clinical Research Center for the Study of Depression in Later Life, located at Duke University (7). All patients with a diagnosis of major depressive disorder who had no comorbid dementia or other major neurological disorders, whose depression was not secondary to medications (e.g., steroids) or medical illnesses, and for whom brain MRI data were available were eligible for the study (N=156). As an additional safeguard against the confounding effect of cognitive impairment, patients with low-to-moderate scores on the Mini-Mental State scale (errors ≥4) (N=26) were removed from the study group. Data on age at onset were not available for 15 patients; these were dropped from further analysis. Missing values for age at onset were distributed similarly across patients with vascular and nonvascular depression. Of the remaining 115 patients, 89 had unipolar disorder and constituted the study group. Seventy-three of

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TABLE 1. Risk Factors Among Patients With Vascular and Nonvascular Depression

Risk Factor	All Patients (N=89)		Patients With Vascular Depression (N=37)		Patients With Nonvascular Depression (N=52)		Analysis[a]	
	N	%	N	%	N	%	Odds Ratio	95% Confidence Interval
Age (years)								
≥60	39	43.8	27	73.0	12	23.1		
<60	50	56.2	10	27.0	40	76.9		
Sex							0.87	0.30–2.51
Female	61	68.5	26	70.3	35	67.3		
Male	28	31.5	11	29.7	17	32.7		
Family history of mental illness							0.84	0.30–2.35
Yes	59	66.3	22	59.5	37	71.2		
No	30	33.7	15	40.5	15	28.8		
Family history of suicide							0.58	0.20–1.72
Yes	27	30.3	9	24.3	18	34.6		
No	62	69.7	28	75.7	34	65.4		
Family history of alcohol or drug use							1.53	0.55–4.29
Yes	45	50.6	18	48.6	27	51.9		
No	44	49.4	19	51.4	25	48.1		
Psychotic features							0.17	0.03–0.99
Yes	12	13.5	2	5.4	10	19.2		
No	77	86.5	35	94.6	42	80.8		
Loss of interest							1.40	0.45–4.34
Yes	66	74.2	29	78.4	37	71.2		
No	23	25.8	8	21.6	15	28.8		
Motor retardation							0.77	0.22–2.67
Yes	72	80.9	30	81.1	42	80.8		
No	17	19.1	7	18.9	10	19.2		
Guilt feelings							1.11	0.36–3.43
Yes	67	75.3	28	75.7	39	75.0		
No	22	24.7	9	24.3	13	25.0		
Age at onset (years)							3.35	1.02–10.97
>40 (late)	30	33.7	22	59.5	8	15.4		
≤40 (early)	59	66.3	15	40.5	44	84.6		
Number of episodes							1.66	0.52–5.32
>12	23	25.8	9	24.3	14	26.9		
≤12	66	74.2	28	75.7	38	73.1		
Montgomery-Åsberg Depression Rating Scale score							1.42	0.53–3.79
≥30	49	55.1	23	62.2	26	50.0		
<30	40	44.9	14	37.8	26	50.0		
Instrumental activities of daily living score							4.07	0.91–18.13
≥10	14	15.7	11	29.7	3	5.8		
<10	75	84.3	26	70.3	49	94.2		
Vascular symptoms							1.04	0.23–4.76
Yes	10	11.2	6	16.2	4	7.7		
No	79	88.8	31	83.8	48	92.3		

[a]Age-adjusted odds of risk factor among patients with vascular depression.

the 89 subjects had recurrent unipolar depression; 12 had psychotic features; six had a history of chronic obstructive pulmonary disease; six had a history of emphysema; none was diabetic; 15 had hypertension; 10 had cardiac disease; four had a history of alcohol dependence. The procedures and purpose of the study were explained to all patients and written informed consent was obtained from each.

Measures

Case status. MRI acquisition procedures were as follows: all subjects were screened by a technologist for presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other circumstance where MRI is contraindicated. Any such subjects were excluded from the study. Physicians (K.R.R.K. or another physician) conducted preliminary interviews with the screened subjects, explaining the MRI examination. The subjects wore patient gowns during scanning to eliminate any external ferromagnetic contaminants (e.g., snaps, zippers, hairpins, or bra underwire).

The standardized section of the MRI study used T_1- and T_2-weighted ^1H spin-echo pulse sequences to image the subject's brain in the head coil of the MRI system. The landmark of the imaging volume was the nasion. Calibration standards for T_2 (80- and 120-msec T_2 values) were included within the field of view. The first set of images were obtained with an axial multisection long TR (2500–3000 msec) double-echo (30–40 and 75–80 msec) spin-echo data-acquisition sequence with flow compensation gradients, 256 phase-encoding steps. To obtain enough sections to cover the whole brain, 5-mm-thick with 2.5-mm-gap acquisitions were used. Saturation of spins outside the imaging volume (standard gap=15 mm) and flow compensation (gradient moment nulling) were used routinely to eliminate artifacts due to flowing blood and CSF. This was followed by a series of T_1-weighted images (TR=500 msec, TE=20 msec) with a 256×192 matrix, 5-mm section thickness with 2.5-mm gap. Aliasing in the phase-encoding and frequency-encoding axes was eliminated if necessary by oversampling and filtration. These two sequences formed a "minimal" routine brain examination that is adequate for

reference to clinical care standards and location of lesions but that needed additional sequences for good volume measurement and further characterization of lesions.

Lesions were classified according to a modified Fazekas classification system (8, 9), which provides a rough assessment of the extent of subcortical gray matter, deep white matter, and periventricular changes on brain MRI. Patients were classified as having vascular depression if they had a score of 2 or more on either deep white matter hyperintensity or subcortical gray matter ratings. Comparison subjects (those whose depression was nonvascular) had scores of 0 or 1 on both the deep white matter hyperintensity and subcortical gray matter ratings. A single punctate lesion in deep white matter reflects perivascular space and is considered normal; thus, the classification was based on a conservative interpretation. The large lesions correlated with areas of myelin pallor, infarcts, or lacunae (9). The ratings were conducted blind to clinical information. The intraclass correlation coefficient (ICC) for deep white matter hyperintensity was 0.85; for subcortical gray matter ICC=0.80.

Risk factors. All patients were given the Duke Depression Evaluation Schedule (7), a composite diagnostic interview instrument that includes the Center for Epidemiologic Studies Depression Scale, the Carroll Rating Scale, the NIMH Diagnostic Interview Schedule (DIS), and the Montgomery-Åsberg Depression Rating Scale. The instruments included were used separately and were enriched with items permitting diagnosis of all disorders in DSM-III and DSM-III-R, including major depressive episode, its subtypes, and comorbid psychiatric conditions (e.g., generalized anxiety, panic, and somatization disorders).

Data on all risk factors were taken from the Duke Depression Evaluation Schedule. Several of the clinical risk factors, such as age at onset, number of depressive episodes, symptoms of depression (apathy, guilt feelings, motor retardation), and subtype (psychosis), were obtained with the DIS section that assesses depression. The interrater reliability for most DIS items was 1.0, reflecting the extremely structured format of the Duke Depression Evaluation Schedule. Patients were subdivided into those with early-onset and late-onset depression by using age 40 as the cutoff. Cutoffs of 45 and 50 years were also examined. Excess risk for number of episodes was counted for patients with episodes in the highest quintile (>12). Information on family history of suicide, alcohol or drug abuse, and other mental illness was also obtained from the patients in the study. The reliability for family history of suicide was 0.83, based on a blind reassessment of videotaped interviews. Severity of depression was assessed by using the Montgomery-Åsberg Depression Rating Scale; patients were considered at high risk if their total score was 30 or higher.

Medical vascular risk was assessed as positive if the patient reported heart disease with history of hypertension or stroke or a history of hypertension and stroke. The measure of disability included nine self-reported instrumental activities of daily living items that assessed gross mobility and cognitive function (e.g., shopping and managing household finances). Instrumental activities of daily living risk was counted as positive for patients with disability scores in the highest quintile (≥10).

Analysis

Differences in risk factors between patients with vascular and nonvascular depression were examined initially with chi-square tests of differences in proportions and subsequently with logistic regression models of the vascular risk associated with each individual risk factor, adjusted for age only. No colinearity problems were evident among independent variables. A multivariable logistic regression model was also tested with all potential risk factors in the model. The relationship of risk factors to brain lesions measured as continuous variables was also examined.

TABLE 2. Multiple Logistic Regression Parameters for Comparison of 37 Patients With Vascular Depression and 52 Patients With Nonvascular Depression[a]

Risk Factor	Parameter Estimate	Standard Error	Odds Ratio	95% Confidence Interval
Age ≥60	–1.71	0.78	0.18	0.04–0.83
Female	0.03	0.65	1.03	0.29–3.72
Family history of mental illness	–1.02	0.72	0.36	0.09–1.48
Family history of suicide	–0.57	0.79	0.57	0.12–2.69
Family history of alcohol or drug use	1.49	0.79	4.42	0.94–20.88
Psychotic features	–2.52	1.16	0.08	0.01–0.79
Loss of interest	1.22	0.83	3.37	0.66–17.30
Motor retardation	–1.71	1.04	0.18	0.02–1.38
Guilt feelings	1.05	1.03	2.87	0.38–21.62
Late onset (>40 years)	1.97	0.87	7.16	1.30–39.45
Number of episodes >12	0.26	0.83	1.30	0.26–6.58
Montgomery-Åsberg Depression Rating Scale score ≥30	0.26	0.77	1.30	0.29–5.88
Instrumental activities of daily living score ≥10	1.40	0.93	4.04	0.65–25.08
Vascular symptoms	0.44	0.97	1.55	0.23–10.44

[a]–2 log likelihood χ^2=77.24, df=14, p=0.0001.

RESULTS

The distribution of risk factors in the patients with vascular and nonvascular depression is presented in table 1. Patients with vascular depression were more likely to be at least 60 years old than were patients with nonvascular depression (χ^2=21.9, df=1, p=0.001). In age-adjusted analyses, patients with vascular depression demonstrated higher odds of having nonpsychotic subtypes of depression and of having late-onset depression (>40 years) when the cutoff for age at onset was 40 years, but not when it was 45 or 50 years. In analyses adjusted only for age, vascular brain changes were not significantly disproportionate across the items of gender, family history of mental illness, depressive subtype, symptoms associated with the index episode, number of episodes, symptom severity, functional disability, or medical history of vascular problems. The relationship between age at onset and severity of hyperintensity was nonlinear when age was controlled for.

In fully controlled analyses (table 2), patients with vascular depression demonstrated significantly higher odds of being elderly, nonpsychotic, and having a late-onset depressive disorder. In addition, the odds of a family history of alcohol or drug abuse, functional disability, and anhedonia were greater than four or three times those of the patients with nonvascular depression (table 2). However, the confidence intervals associated with these odds ratios demonstrated that chance cannot be excluded as the reason for differences in the proportions. The number of subjects limits the precision of these estimates. Cognitively impaired subjects demonstrated more cardiovascular comorbidity and a trend toward more hyperintensities. Hyperintensities were more frequent in older men than in younger men or older women.

We also regressed continuously distributed scores for deep white matter hyperintensity over all risk factors in ordinary least squares models. Age, family history of

alcohol use, and nonpsychotic subtype were strongly significant risk factors. Other risk factors were in the direction of hypothesized relationships (data not shown).

DISCUSSION

The present study of a relatively large number of depressed patients whose vascular or nonvascular depression was determined by MRI provides limited support for all five hypotheses. We found that both crude and adjusted risks of vascular depression were associated with age and late-onset depressive illness. These results validate earlier studies showing a link between vascular changes and late-onset depression (10–14). Lower risk of a family history of mental disorder or suicide and higher risk of anhedonia and functional disability were evident among patients with vascular depression, although chance cannot be ruled out as the explanation. The lack of significance may be related to an insufficient number of subjects and also the lack of clinically significant differences in these variables. The results of this study may reflect a unique group of patients who seek evaluation in a clinical research center. Further studies in larger numbers of patients are needed to expand on these initial results. The findings also suggest that depression—even in patients with cerebrovascular changes—is probably multifactorial and that genetic factors and life events continue to be important. The genetic factors in this group of patients may be different and could be related to the genetic risk factors for vascular disease.

The concept of vascular depression is subject to the same limitations as the concept of vascular dementia. The major problem with these concepts is that they presuppose that vascular factors are the sole cause of the syndrome. In the case of vascular dementia there is increasing recognition that vascular factors are often contributors even though they may not be the primary cause of the cognitive deficits (15–17). In a similar vein, we have speculated that depression in patients with cerebrovascular disease is also multifactorial in origin and that vascular factors are but one etiologic factor. In the case of vascular dementia, treatment of vascular risk factors has not been shown to provide cognitive improvement (18). To a certain extent, the findings affirm the effects of coexisting cerebrovascular disease, i.e., increased disability. At the current time there are limited data suggesting that treatment response is different in these patients (19). We are in the process of completing long-term outcome studies that could supplement the limited data now available. It is possible that treatment of vascular risk factors may be of benefit in patients with vascular depression.

We have suggested that depression in these patients may be the result of damage to the striato-pallido-thalamo-cortical pathways (20). The damage due to the lesions may cause depression either by means of direct disruption of the circuits regulating mood or disruption of the norepinephrine and serotonin circuits that regulate this system. Studies evaluating monoamine function and functional imaging studies may provide further exposition of the pathophysiology of vascular depression.

The concept of vascular depression may have diagnostic, prognostic, and treatment implications. Further studies are needed to evaluate if the cause of illness, disability, and cognitive impairment is different in these patients. The demonstration by recent epidemiologic studies that the type of vascular changes seen in the brain are related to carotid atherosclerosis, hypertension, and history of myocardial infarcts (21, 22) also points to the need for evaluating vascular risk more closely in these patients and designing suitable treatment regimens to reduce these risk factors. Treatment could include regimens such as a low-fat, low-salt diet, use of suitable pharmacological strategies to control high cholesterol or hypertension, and surgical techniques to treat carotid atherosclerosis.

REFERENCES

1. Mendlewicz J, Baron M: Morbidity risks in subtypes of unipolar depressive illness: differences between early and late onset forms. Br J Psychiatry 1981; 139:463–466
2. Coffey CE, Figiel GS, Djang WT: Leukoencephalopathy in elderly depressed patients referred for ECT. Biol Psychiatry 1988; 24:143–161
3. Lesser IM, Miller BL, Boone KB: Brain imaging and cognitive function in late-onset psychotic depression. J Neuropsychiatry 1991; 3:33–40
4. Fujikawa T, Yamawaki S, Touhouda Y: Incidence of silent cerebral infarction in patients with major depression. Stroke 1993; 24:1631–1634
5. Krishnan KRR, McDonald WM: Arteriosclerotic depression. Med Hypotheses 1995; 44:77–145
6. Fazekas F, Chawluk JB, Alavi A: MR signal abnormalities at 1.5T in Alzheimer's dementia and normal aging. AJNR Am J Neuroradiol 1987; 8:421–426
7. Krishnan KRR, Hays JC, Tupler LA, George LK, Blazer DG: Clinical and phenomenological comparisons of late-onset and early-onset depression. Am J Psychiatry 1995; 152:785–788
8. Greenwald BS, Kramer-Ginsberg E, Krishnan KRR, Ashtari M, Aupperle PM, Patel M: MRI signal hyperintensities in geriatric depression. Am J Psychiatry 1996; 153:1212–1215
9. Krishnan KRR, Boyko OB, McDonald WM, Charles HC, MacFall J, Tupler LA, Upchurch L: Magnetic resonance morphometry: image analysis methodology development for affective disorder. Depression 1993; 1:159–171
10. Coffey CE, Figiel GS, Djang WT, Saunders WB, Weiner RD: White matter hyperintensity on MRI clinical and neuroanatomic correlates in the depressed elderly. J Neuropsychiatry Clin Neurosci 1989; 1:135–144
11. Coffey CE, Figiel GS, Djang WT, Weiner RD: Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. Am J Psychiatry 1990; 147: 187–189
12. Figiel GS, Krishnan KRR, Doraiswamy PM, Rao VP, Nemeroff CB, Boyko OB: Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. Neurobiol Aging 1991; 26:245–247
13. Zubenko GS, Sullivan P, Nelson JP, Belle SH, Huff FJ, Wolf GL: Brain imaging abnormalities in mental disorders of late life. Arch Neurol 1990; 47:1107–1113
14. Rabins PV, Pearlson GD, Aylward E, Kumar AJ, Dowell K: Cortical magnetic resonance imaging changes in elderly inpatients with major depression. Am J Psychiatry 1991; 148:617–620
15. Geldmacher DS, Whitehouse PJ: Multi infarct dementia, in Psy-

chopharmacology: The Fourth Generation of Progress. Edited by Bloom FE, Kupfer DJ. New York, Raven Press, 1993, pp 1513–1520
16. Brust JCM: Vascular dementia is overdiagnosed. Arch Neurol 1988; 45:799–801
17. O'Brien MD: Vascular dementia is underdiagnosed. Arch Neurol 1988; 45:797–798
18. Meyer JS, Judd BW, Tawakma T, Rogers RL, Mortel KF: Improved cognition after control of risk factors for MID. JAMA 1986; 256:2203–2209
19. Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B: Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry 1995; 37:151–160
20. Krishnan KRR: Neuroanatomic substrates of depression in the elderly. J Geriatr Psychiatry Neurol 1993; 1:39–58
21. Bots ML, van Swieten JC, Breteler MM, de Jong PT, van Gijn J, Hofman A, Grobbee DE: Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993; 341:1232–1237
22. Manolio TA, Kronmal RA, Burke GL, Poirier V, O'Leary DH, Gardin JM, Fried LP, Steinberg EP, Bryan RN: Magnetic resonance abnormalities and cardiovascular disease in older adults: the Cardiovascular Health Study. Stroke 1994; 25:318–327

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