Clinically Defined Vascular Depression

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Objective: The authors' goal was to examine the clinical presentation of a group of depressed elderly patients with clinically defined risk factors for vascular depression compared with a group of elderly depressed patients without such risk factors. Method: Cognitive deficits, disability, and depressive symptoms were examined in 33 consecutively recruited elderly patients defined as having vascular depression and 32 patients defined as having nonvascular depression according to their scores on the Cumulative Illness Rating Scale—Geriatrics. Results: The patients with vascular depression had greater overall cognitive impairment and disability than those with nonvascular depression. Fluency and naming were more impaired in patients with vascular depression, and they had more retardation and less agitation as well as less guilt feelings and greater lack of insight. Conclusions: The symptoms of vascular depression are consistent with lesions that may damage striato-pallido-thalamo-cortical pathways and other areas. The concept of vascular depression can provide the impetus for investigations of prevention and treatment of cerebrovascular disease and for studies of the course of vascular depression and selection of antidepressants.

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In 1990, we proposed that late-onset depression encompasses a high percentage of patients with neurological brain disorders (1). The studies of Krishnan and McDonald (2, 3) suggested that cerebrovascular disease may contribute to the development of a late-onset depression syndrome. The vascular depression hypothesis is supported by 1) the high rate of depression in patients with hypertension, diabetes, and coronary disease (4, 5), 2) the high rate of depression in patients who have had a stroke (6, 7), 3) the frequent occurrence of silent stroke and white matter hyperintensities in late-onset depression (8–11), and 4) the infrequent family history of mood disorders in depression occurring in the context of silent stroke (12).

Cerebrovascular lesions usually occur at areas receiving blood from perforating arteries supplying the basal ganglia or at the borders of vascular territories (8). For this reason, patients with vascular risk factors may have lesions at the basal ganglia. Damage of the basal ganglia and their connections to prefrontal structures has been associated with depression as well as a frontal lobe syndrome that includes retardation, lack of insight, and impaired executive functions (13). Therefore, we would expect vascular depression to be accompanied by these symptoms and signs. Since vascular lesions usually are not limited to the basal ganglia and the prefrontal areas, a broader spectrum of cognitive impairments and disability may occur in vascular depression.

This study examines whether a clinically defined group likely to include patients with vascular depression had a different clinical presentation from that of a group of patients who were less likely to include patients with vascular depression. Our hypothesis was that vascular depression is accompanied by greater cognitive dysfunction, disability, retardation, and lack of insight and less agitation and depressive ideation than is nonvascular depression.

METHOD

We studied two groups of consecutively recruited elderly patients (60 years or older) with major depression diagnosed according to Research Diagnostic Criteria (14). All subjects provided written informed consent. One group of patients—those defined as having vascular depression—experienced the first onset of depression at 60 years of age or older and had a vascular score of 1–4 on the Cumulative Illness Rating Scale—Geriatrics (15). On this scale a score of 0=no hypertension, 1=hypertension compensated with diet, 2=taking antihypertensive medications, 3=two or more stigmata of atherosclerosis, and 4=history of transient ischemic attack or surgery for vascular disease. The other group—those defined as having nonvascular depression—experienced the first onset of depression earlier than 60 years of age and had a Cumulative Illness Rating Scale—Geriatrics score of 0.

Exclusion criteria were 1) psychiatric disorders (except personality disorder) before the first depressive episode; 2) metastatic cancer, de-

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TABLE 1. Demographic and Clinical Characteristics of Elderly Patients With Vascular and Nonvascular Depression[a]

Variable	Patients With Vascular Depression (N=33)			Patients With Nonvascular Depression (N=32)		
	N	Mean	SD	N	Mean	SD
Age (years)[b]	33	74.4	5.9	32	71.5	6.7
Disability (Multilevel Assessment Instrument score)	33	4.0	0.9	32	4.8	0.5
Dementia Rating Scale						
Total score	32	130.4	10.1	32	138.1	4.9
Fluency (words from C, F, or W in 1 minute [21])	32	35.9	10.9	32	41.1	9.6
Visual retention (recognition of Benton visual stimulus cards from a matrix of four cards)	29	6.2	2.1	26	7.8	1.9
Verbal memory (d′ from 14-item Mattis-Kovner scale [22])	31	2.4	1.0	32	2.7	0.7
Comprehension (tokens of two shapes, two sizes, and five colors [20])	30	13.7	3.1	28	15.0	1.3
Visual naming (identification of 30 line drawings [21])	33	48.2	8.8	32	52.3	6.5
Construction: drawing clock (% abnormal)	33	36.3	27.6	32	15.6	20.5
Construction: copying Bender-Gestalt hexagon (% abnormal)	33	33.3	27.1	32	12.5	20.0
17-item Hamilton Depression Rating Scale						
Total score	33	25.96	6.76	32	27.00	5.95
Retardation	33	0.79	1.10	32	0.34	0.70
Agitation	33	0.12	0.33	32	0.41	0.61
Guilt feelings	33	1.03	0.92	32	1.50	0.72
Lack of insight	33	0.42	0.61	32	0.19	0.47

[a]The ratio of women to men in the group with vascular depression was 2.3:1, and in the group with nonvascular depression it was 1.5:1 (χ^2=0.75, df=1, n.s.).
[b]t=1.88, df=63, p<0.07.

compensated cardiac, hepatic, or renal failure, and stroke with neurological signs; 3) delirium, probable Alzheimer's disease (according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [16]), Huntington's chorea, or Parkinson's disease; 4) complete impairment in activities of daily living (defined by the Multilevel Assessment Instrument [17] as needing help throughout the day and night); and 5) Mini-Mental State (18) score lower than 17. These criteria allowed study of a group of patients with substantial impairments.

Depressive symptoms, disability, and overall cognitive impairment were rated with the 17-item Hamilton Depression Rating Scale (19), the Multilevel Assessment Instrument (17), and the Dementia Rating Scale (20), respectively. Specific cognitive dysfunctions were rated: for fluency, words from C, F, or W in 1 minute (21); for verbal recognition, the Mattis-Kovner scale (22); for visual retention, recognition of Benton stimulus cards from a matrix of four cards; for language comprehension, operations using tokens of two shapes, two sizes, and five colors (20); for visual naming, identification of 30 line drawings (21); and for construction, drawing a clock and copying the Bender-Gestalt hexagon picture.

Data were analyzed with t tests and chi-square. When potentially nonindependent variables were compared, exploratory principal components analysis with varimax rotation was first used to identify related variables; factors with an eigenvalue greater than 1.0 were extracted. Then, multivariate analysis of covariance (MANCOVA) was used to examine group differences among factors. Two-tailed significance is reported.

RESULTS

We studied a total of 65 patients; 33 were classified as having vascular depression and 32 as having nonvascular depression. Gender was distributed similarly in the two groups (table 1). There was a trend toward older age in the patients with vascular depression (table 1). For this reason, age was used as a covariate in all analyses.

Exploratory principal component analysis using the Hamilton depression scale items retardation, agitation, guilt feelings, and lack of insight identified two factors (58% of the variance). A retardation/agitation factor predicted 31% of the variance (eigenvalue=1.24), and a guilt feelings/lack of insight factor predicted 27% of the variance (eigenvalue=1.08). MANCOVA using age as a covariate showed that disability, Dementia Rating Scale score, retardation/agitation, and guilt feelings/lack of insight were different in the two groups (Wilks's lambda F=8.99, df=4, 58, p<0.0001). Each variable contributed significantly (disability: F=13.52, df=1, 61, p<0.0005; Dementia Rating Scale: F=11.96, df=1, 61, p<0.001; retardation/agitation: F=5.59, df=1, 61, p<0.02; guilt feelings/lack of insight: F=4.53, df=1, 62, p<0.04).

Impairment in specific cognitive functions was studied after conversion to t scores using data of 31 normal subjects aged 60 to 85 years. Since neuropsychological test results may be interrelated, exploratory principal component analysis was used; this identified two factors (56% of the variance). A comprehension/construction factor (language comprehension and construction, eigenvalue=2.7) predicted 38% of the variance. A fluency/naming factor (fluency, visual naming, and visual retention, eigenvalue=1.2) accounted for 18% of the variance. MANCOVA using age as covariate showed that both factors distinguished the two groups (Wilks's lambda F=3.60, df=2, 49, p<0.04). Fluency/naming was more impaired in the patients with vascular depression than in the patients with nonvascular depression (F=5.4, df=1, 50, p<0.02); there were no differences between the patient groups in comprehension/construction (F=1.22, df=1, 50, p<0.28).

DISCUSSION

The principal finding of this study is that late-onset depression associated with vascular risk factors is char-

acterized by cognitive dysfunction, disability, retardation, lack of insight, and limited depressive ideation. To our knowledge, this study is the first to report differences in the presentation of patients with clinically defined vascular depression from that of patients with nonvascular depression. These observations parallel the behavioral abnormalities of vascular dementia, which often consist of depressed mood, motor retardation, emotional withdrawal, and low motivation (23).

The cognitive impairment, retardation, lack of insight, and disability of vascular depression may have resulted from lesions unrelated to depression. However, these symptoms resemble a frontal lobe syndrome that may have resulted from disruption of striato-pallido-thalamo-cortical pathways (2, 3, 13). Damage in these areas frequently occurs in cerebrovascular disease (8–11). Dysfunction of striato-pallido-thalamo-cortical pathways may lead to depression by one or more of the following mechanisms: 1) direct damage of the orbitofrontal, dorsolateral, and anterior cingulate pathways (3, 13); 2) impairment of monoaminergic fibers ascending from the brainstem that disrupts regulation of striato-pallido-thalamo-cortical pathways (3, 7); and 3) impairment of basal ganglia pathways leading to dysfunction of the orbitofrontal pathway and disruption of prefrontal control on the serotoninergic raphe nuclei (24). Although depression may be partly mediated by these mechanisms, vascular risk factors often lead to lesions in other areas. The widespread nature of vascular lesions may explain the broad range of cognitive impairment in this group of patients.

The clinical description of patients with vascular depression may have diagnostic and prognostic significance. Clinicians should assess such patients thoroughly for cognitive impairment and disability and plan their management accordingly.

This study used a clinical definition to identify the group of patients with a high chance of having vascular depression. Since the etiology of depression is unknown, it is impossible to establish that depression in any group is a direct consequence of vascular disease. Therefore, the group of patients with vascular depression might have been heterogeneous, although it is likely that it included more patients with vascular disease than the group of patients with nonvascular depression.

The study is limited by the small number of subjects, which allowed only exploratory multivariate analyses. Another limitation is the absence of brain imaging. However, these findings may provide the background for investigations of the relationship between vascular lesions and specific affective and cognitive symptoms in geriatric depression.

This study does not establish a causative relationship between vascular disease and late-onset depression. This can be done only by demonstration of distinct lesions on the striato-pallido-thalamo-cortical pathways or meaningful differences in treatment response, course, and outcomes between patients with vascular and nonvascular depression. Nonetheless, the concept of vascular depression can provide the impetus for studies of drugs used in the prevention and treatment of cerebrovascular disease. These include anticholisterinemic and antiplatelet agents, free radical scavengers, calcium channel blockers, glutamate *N*-methyl-D-aspartic acid receptor antagonists, gangliosides, aminosteroids, and amphetamine (25). Animal studies suggest that some antidepressants promote neurological recovery after ischemic lesions but that other antidepressants, as well as haloperidol, phenytoin, and benzodiazepines, inhibit recovery (25, 26). It is possible that vascular depression requires a psychopharmacological approach different from that for nonvascular depression. Therefore, if the syndrome of vascular depression is validated, identification of its clinical profile may prove relevant for treatment decisions.

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