

Are Multiple Cerebral Infarcts Synergistic?

Nicola Wolfe, PhD; Viken L. Babikian, MD; Richard T. Linn, PhD; Janice E. Knoefel, MD; Mark D'Esposito, MD; Martin L. Albert, MD

Objective: The goal of this study was to characterize the cumulative effects of multiple strokes on cognition.

Design: We conducted a prospective, longitudinal case study with neuropsychological, neurological, and radiological evaluations.

Setting: Research was conducted at the Boston (Mass) Veterans Administration Medical Center, Neurology Service, on successive inpatient hospital admissions.

Patient: We followed up a 66-year-old right-handed man with multiple subcortical lacunae during a 3.5-year period during which he suffered two additional cortical infarctions.

Main Outcome Measures: Each evaluation included approximately 3 hours of neuropsychological testing spanning a range of cognitive domains (attention, language, memory, visuospatial functions, response inhibition, and mental flexibility), full neurological examination, and computed tomographic scan.

Results: The patient's stepwise cognitive decline was characterized by unexpected exacerbation of "frontal" neurobehavioral features following the occurrence of two posterior cortical lesions. At initial evaluation, the computed tomographic scan showed bilateral subcortical lacunae in basal ganglia and periventricular white matter, and symptoms included dysarthria and perseveration. The second evaluation, following a left posterior parietal lesion, revealed a range of new frontal features, including impulsivity, pull-to-stimulus, and difficulty shifting set. Following a subsequent right occipital infarct, further frontal lobe impairments emerged: forced grasp reflex and incontinence.

Conclusions: We hypothesize that the cumulative effects of infarcts were synergistic. That is, the posterior cortical infarcts elicited frontal features that would not be expected from a simple sum of these lesions' effects.

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THE CUMULATIVE effects of multiple strokes on cognition have proved difficult to characterize. While single infarctions have been clearly

associated with specific neurobehavioral syndromes,¹ cases of multiple lesions have been more difficult to describe due to individual differences in the number, the extent, and the location of lesions. Hachinski² has noted that although the effects of multiple lesions on mental function depend on size, site, number, and nature of lesions, their cumulative effects seem not to be simply additive.

To characterize the longitudinal course of cognitive decline with multiple infarcts, we conducted a prospective, longitudinal study of a 66-year-old, right-handed man with multiple subcortical lacunae during a 3.5-

year period in which he suffered two additional cortical infarctions.

REPORT OF A CASE

The patient, a retired postal worker with a seventh-grade education, was first seen at age 66 years after a Veterans Administration Medical Center admission for sudden onset of light-headedness, slurred speech, and unsteady gait. The medical history was significant for hypertension and

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From the Department of Neurology, University of California at Davis, School of Medicine, and the Northern California Alzheimer's Disease Center, Berkeley (Dr Wolfe); Department of Neurology, Boston (Mass) University School of Medicine and Boston Veterans Administration Medical Center (Drs Babikian, Knoefel, D'Esposito, and Albert); and the Department of Psychiatry, State University of New York at Buffalo, School of Medicine (Dr Linn).

METHODS

The patient was followed up at the Boston (Mass) Veterans Administration Medical Center's Neurology Service with neuropsychological evaluations on May 6, 1987; August 9, 1989; and November 20, 1990 (periods 1 through 3, respectively). Research neuropsychological evaluations were conducted using a battery specifically developed for a study of multi-infarct dementia and have been described previously.³ Each evaluation included approximately 3 hours of neuropsychological testing spanning a range of cognitive domains, including the following: attention/concentration, language, memory, visuospatial functions, response inhibition, and mental flexibility. Tests of attention included an Auditory Continuous Performance Test⁴ and Digit Span (from the Wechsler Adult Intelligence Scale-Revised⁵). Memory testing included the California Verbal Learning Test (nine-word dementia version)⁶; visuoconstructional tasks included drawing of clock, daisy, and cube

to command and to copy⁷; and language evaluations included the Boston Naming Test (15-item version)⁸ and the Controlled Oral Word Association Test.⁹ Measures of response inhibition included Reciprocal Motor Programs¹⁰ and the Stroop Test.¹¹ Ability to shift mental set was assessed using the Visual-Verbal Test (10-item version).¹² The Center for Epidemiologic Study of Depression Scale¹³ was used to measure depressive symptoms. The Mini-Mental State examination¹⁴ and the Barthel Functioning Index¹⁵ were indexes of overall cognitive functioning and daily functioning, respectively. Full neurologic examinations were also performed at each period.

Computed tomographic (CT) scans were performed as part of the patient's clinical evaluation and preceded neuropsychological testing by 1 to 4 months. Thus, the subject was not tested during the short-term recovery period following a stroke. Approximately twelve 7-mm thick slices were obtained per CT. Lacunae were defined as small (<2 cm in maximum diameter), well-circumscribed, subcortical areas of low attenuation consistent with cerebral infarction.¹⁶

mild hyperlipidemia, but the patient was not diabetic. The CT scan for period 1 in April 1987 is shown in **Figure 1**. It revealed evidence of four subcortical lacunar infarcts in the following locations: right periventricular white matter, left periventricular white matter, left external capsule/head of caudate, and right border of putamen and globus pallidus. In addition, the ventricles were moderately enlarged bilaterally, but radionuclide cisternogram (March 1989) for normal pressure hydrocephalus was negative.

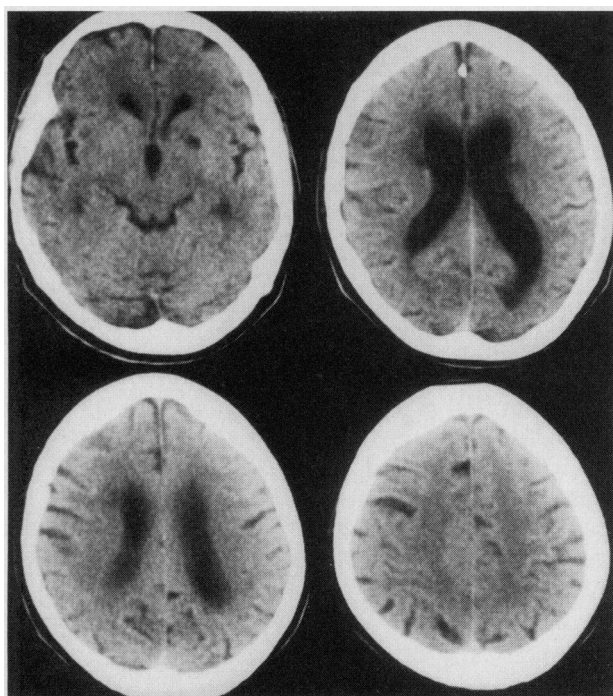


Figure 1. Computed tomographic scan for period 1, April 1987.

Throughout the follow-up period, findings from the cardiac examination remained unremarkable. Electrocardiogram showed regular pulse with a left bundle branch block. An echocardiogram and an electroencephalographic study were within normal limits. Noninvasive studies of the carotid arteries showed findings consistent with less than 50% stenosis bilaterally in April 1987 and April 1988.

During the 3.5-year follow-up, the patient was readmitted to the hospital with clinical symptoms of two further incidents of cerebral infarction. The CT scan for period 2 was performed in April 1989 (**Figure 2**). In addition to the multiple subcortical lacunae, it showed a left cortical parietal area of low attenuation with deep white matter extension. **Figure 3** shows the CT scan for period 3, performed in July 1990. In addition to the four subcortical lacunae and the left parietal cortical lesion, a new right-sided occipital polar lesion of moderate size was present. Progression of ventricular enlargement, cortical atrophy, and white matter changes was also observed. A summary of neuropsychological results over three periods is shown in the **Table**.

Although cognitive decline covered a broad range of domains, including attention, language, memory, and visuospatial functions, the most salient change was the emergence of "frontal" features in periods 2 and 3. The course of cognitive decline was stepwise, paralleling clinical symptoms of infarction. After the left parietal infarct, notable increases were seen in impulsivity. The number of impulsive errors on auditory continuous performance test (tapping after X alone on auditory XIs) increased from 1 to 13. Also at period 2, the patient demonstrated pull-to-stimulus, for example, drawing on top

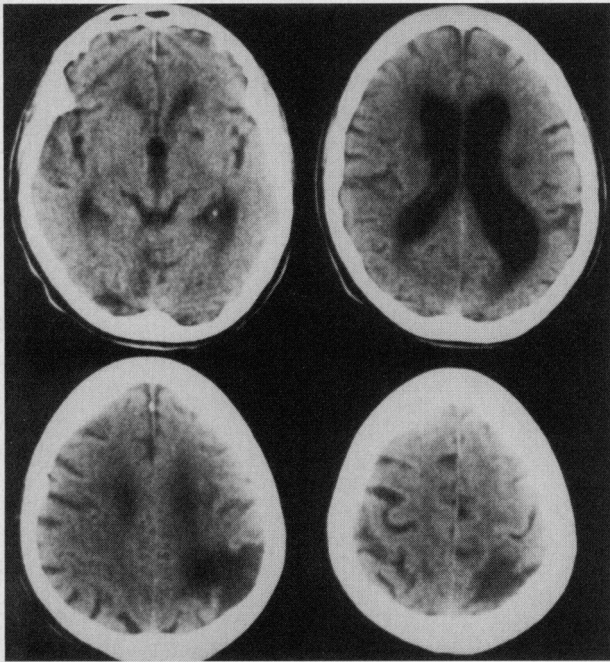


Figure 2. Computed tomographic scan for period 2, April 1989.

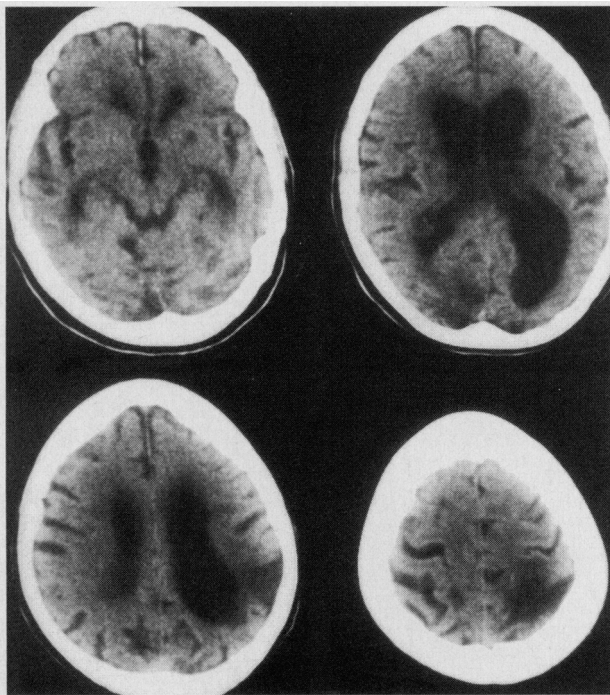


Figure 3. Computed tomographic scan for period 3, July 1990.

of figures to be copied. Poor response inhibition was noted on the Stroop Test color-interference condition where his score declined from 38 to 10. Also, on reciprocal motor programs, errors of imitation increased from 2 to 33. He exhibited difficulty shifting mental set on the Visual-Verbal Test, with the score declining from 100% shifted to only 28% shifted. It was at period 2 that the patient dropped below the dementia cutoff score of 24 on the Mini-Mental State examination and also met research cri-

teria for probable ischemic vascular dementia.¹⁷ Following the additional occipital cortical lesion, period 3, further deterioration included a return of forced grasp reflex and urinary and fecal incontinence. Depressive symptoms, as measured by the Center for Epidemiologic Study of Depression Scale, were less pronounced in periods 2 and 3 than in period 1.

COMMENT

This patient suffered multifocal cognitive decline, with the emergence of frontal symptoms following additional posterior cortical lesions. It is this unexpected pattern that leads us to suggest the hypothesis that multiple infarcts may have a "synergistic" effect. The term *synergy* is used here to mean that the combined effect of lesions yields a pattern of deficits different from that which would be predicted by simply summing individual lesion effects. Specifically, the posterior cortical infarcts were associated with development of frontal neurobehavioral features. This phenomenon, which we are labeling "synergistic," has been noted by other investigators. Hachinski,² for example, noted the following: "In general, the effect of additional lesions of the brain increases with the number of lesions already present, so that deficits in the brain do not merely add up, they multiply."

Interpretation of this case must also consider alternative neuropathological and neuropsychological explanations. In addition to posterior cortical lesions, the CT scans reveal progression of cortical atrophy, ventricular enlargement, and mild leukoaraiosis suggestive of a more diffuse degenerative process. The progression of periventricular white matter abnormalities, including frontal white matter, could in part explain the emergence of frontal behaviors. Although some investigators have noted leukoaraiosis on CT scans to be associated with increased dementia,¹⁸ leukoaraiosis is not necessarily associated with neuropsychological deficits.¹⁹ The severity of dementia in this patient and the time course that corresponds with subsequent cortical infarctions suggest that more than white matter abnormality is involved.

Progressive enlargement of ventricles seen in this patient is unlikely to represent normal pressure hydrocephalus. The radionuclide cisternogram at period 2 was negative, and the clinical profile of normal pressure hydrocephalus (cognitive impairment, incontinence, and gait disturbance) was not present until period 3. More likely, this hydrocephalus ex vacuo was associated with tissue loss secondary to recurrent cerebral infarction. Some investigators²⁰ have observed a correlation between ventricular enlargement and cognitive impairment. Although such a relationship may contribute to cognitive decline seen in this patient, it does not explain the severity or the stepwise pattern of cognitive decline.

An alternative explanation is that following each infarction, some recovery of function occurs through respe-

Neuropsychology Testing Results*

	Period		
	1 (5/87)	2 (8/89)	3 (11/90)
Attention			
Digit span (forward)	6	3	3
Digit span (backward)	5	3	0†
Auditory CPT (XIs) (No. correct /26)‡	22	11	1
Memory			
California Verbal Learning Test (CVLT) (9-word dementia version)			
Maximum correct /9 (trials 1-5)	7	4	5
Immediate free recall	7	1	1
20-minute delayed free recall	7	4	1
Total perseverations (trials 1-5)	1	7	6
Total intrusions (trials 1-5)	1	0	1
Total semantic clusters (trials 1-5)	2	4	3
Visuospatial functions			
Drawing to copy (clock, daisy, cube) /15	13	5	4
Drawing to command (clock, daisy, cube) /15	8	3	3
Language			
Boston Naming Test (15-item version)			
No. correctly named /15	13	12	11
Phonemic paraphasias	2	7	6
Verbal fluency (Controlled Oral Word Association Test)			
Phonemic (total FAS words correct)	28	11	0†
Perseverative repetitions on FAS	3	8	0†
Categories (total: animals, fruits and vegetables, first names)	42	15	10
Perseverative repetition on categories	1	8	8
Dysarthria	Yes	Yes	Yes
Response inhibition			
Impulsivity (tapping prior to X on CPT XIs)	1	13	10
Pull-to-stimulus (drawing on top of figure to be copied)	No	Yes	Yes
Reciprocal motor programs (errors of imitation, maximum 40)	2	33	26
Stroop test (No. correct: color-interference condition)	38	10	0†
Perseveration			
Continuous perseveration (m n m n)	Yes	Yes	Yes
Continuous perseveration (multiple loops)	Yes	Yes	Yes
Shifting mental set			
Visual-Verbal Test (No. of cards correctly shifted/No. correct first trial)	7/7	2/7	0/0†
Behavioral observations			
Sudden onset laughing or crying	No	No	No
Apathy during testing	No	No	No
Urinary and fecal incontinence	No	No	Yes
Forced grasp reflex	No	No	Yes
Overall cognitive functioning			
Mini-Mental State examination	27	11	10
Barthel Functioning Index	100	85	35
Mood			
Center for Epidemiologic Study of Depression Scale (CES-D) /60	39	20	18

*FAS indicates Controlled Oral Word Association Test; CPT, Continuous Performance Test; and CES-D, Center for Epidemiologic Study of Depression Scale.

†Patient was not able to initiate the mental set for this test.

‡Number after virgule indicates the maximum score possible on this test.

cialization of intact neural tissue. Subsequent infarction in that respecialized area could yield behavioral impairments not usually seen following a single lesion in that area. It is considered highly unlikely, however, in this particu-

lar case, that respecialization of infarcted regions could explain the emergence of "frontal lobe" features.

An alternative explanation is the presence of a degenerative disorder such as Alzheimer's disease in addi-

tion to multiple infarctions. The pattern of neuropsychological findings is more characteristic of a frontal lobe dementia than the degeneration of Alzheimer's disease. Although the stepwise course in this case would be uncharacteristic of Alzheimer's disease, this cause cannot be completely ruled out.

In addition, it could be argued that the neuropsychological impairments that emerged are not restricted to the frontal lobes. Difficulties shifting set, impulsivity, and pull-to-stimulus were salient features; however, there was also global cognitive decline. Some functions such as confrontation naming or mood did not decline with time, but deterioration was not entirely restricted to frontal tasks.

Localization of so-called frontal features specifically to the frontal lobes has been increasingly challenged. Recent publications have shown these frontal lobe behaviors to emerge following lesions to a number of areas: left medial thalamus,²¹ paramedian thalamus,²² and head of caudate.²³⁻²⁵ We have noted previously,³ as did Ishii et al.,²⁶ that multiple subcortical lacunae could produce a behavioral profile characteristic of frontal damage. Thus, it may be more appropriate to attribute these symptoms to "frontal systems" damage. Bilateral lacunae in basal ganglia and periventricular white matter could be considered to have interfered with a frontal-subcortical system.²⁷ In this patient, however, the subcortical lacunae were present already in period 1 and cannot explain the progression of frontal neuropsychological findings in periods 2 and 3.

The idea that multiple infarcts combine synergistically is consistent with the model by Mesulam²⁸ of neuronal networks and parallel distributed processing. He has suggested that "complex behavior is mapped at the level of multifocal neural systems rather than specific anatomical sites, giving rise to brain behavior relationships that are both localized and distributed." Although it could be argued that this neuronal network model could explain many unexpected associations between lesions and cognition, the model, nevertheless, provides an anatomic basis for our clinical observation that individual lesion effects do not simply add up but can be synergistic. This case suggests that functions often associated with the frontal lobes, such as response inhibition or complex executive functions, may be emergent properties relying on the intact functioning of widely interconnected systems of neurons, rather than being rigidly localized to the frontal lobes.

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Reprint requests to University of California, Davis—Northern California Alzheimer's Disease Center, Alta Bates Medical Center, 2001 Dwight Way, Berkeley, CA 94704 (Dr Wolfe).

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