How Complex Interactions of Ischemic Brain Infarcts, White Matter Lesions, and Atrophy Relate to Poststroke Dementia

Tarja Pohjasvaara, MD, PhD; Riitta Mäntylä, MD; Oili Salonen, MD, PhD; Hannu J. Aronen, MD, PhD; Raija Ylikoski, PhD; Marja Hietanen, PhD; Markku Kaste, MD, PhD; Timo Erkinjuntti, MD, PhD

Background: Cerebrovascular disease is a major factor related to cognitive impairment. However, behavioral correlates of ischemic brain lesions are insufficiently characterized.

Objective: To examine magnetic resonance imaging correlates of dementia in a large, well-defined series of patients with ischemic stroke.

Methods: Detailed medical, neurological, and neuropsychological examinations were conducted 3 months after ischemic stroke for 337 of 486 consecutive patients aged 55 to 85 years. Infarcts (type, site, side, number, and volume), extent of white matter lesions (WMLs), and degree of atrophy were categorized according to magnetic resonance images of the head. The definition for dementia of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) was used.

Results: Dementia was diagnosed in 107 (31.8%) of the patients and stroke-related dementia in 87 (25.8%). Volumes, numbers, distinct sites of infarcts, extent of WMLs, and degree of atrophy were different for the demented and nondemented subjects. Particularly, volumes of infarcts in any (right- or left-sided) superior middle cerebral artery territory (27.3 vs 13.7 cm³, \(P = .002\)) and left thalamocortical connection (14.8 vs 4.0 cm³, \(P = .002\)) differentiated the 2 groups. Logistic regression analysis showed that the correlates of any dementia included the combination of infarct features (volume of infarcts in any superior middle cerebral artery: odds ratio [OR], 1.11; frequency of left-sided infarcts: OR, 1.21), extent of WMLs (OR, 1.3), medial temporal lobe atrophy (OR, 2.1), and host factors (education; OR, 0.91). In the patients with stroke-related dementia, the main correlate was volume of infarcts in the left anterior corona radiata (OR, 1.68).

Conclusion: Correlates of poststroke dementia do not include merely 1 feature but a combination of infarct features, extent of WMLs, medial temporal lobe atrophy, and host features.

Arch Neurol. 2000;57:1295-1300
SUBJECTS AND METHODS

Procedures of the Helsinki Stroke Aging Memory Study cohort have been detailed in a report on methods and baseline findings. Briefly, 486 consecutive patients aged 55 to 85 years were evaluated 3 months after ischemic stroke. Of the 486 patients, 337 (69.3%) had a completed MRI of the head and a comprehensive neuropsychological examination. The reasons for exclusions as well as comparison of the included and excluded patients are detailed in a previous report. A structured medical and neurological history was recorded based on review of all available hospital charts, an interview of the subject and a knowledgeable informant, and a structured clinical and neurological examination performed by a board-certified neurologist (T.P.) and a senior neurologist (T.E.).

The criteria for dementia were those of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III). Cognitive domains of the DSM-III definition assessed by the neuropsychological test battery included memory functions (short- and long-term memory), executive functions, abstract thinking, judgment, aphasia, apraxia, agnosia, constructional and visuospatial abilities, and personality change. Instead of using the more recent definitions for dementia, we chose the DSM-III definition used in a previous comparative stroke cohort. Assessment of the patient’s ability to work and to perform basic activities of daily life and complex activities of daily life was performed with 5 scales reflecting functions before and 3 months after the index stroke. Assessment of prestroke cognitive impairment was based on interviews with the patient and a knowledgeable informant as described in a previous report. Altogether, 31 patients had prestroke cognitive impairment, and they were excluded from the group with stroke-related dementia (n = 306; demented, n = 87). This accords with definitions used in earlier studies.

Education was divided into 2 categories: low (0-6 years of formal education) and high (>6 years of formal education).

Magnetic resonance imaging was performed with a superconducting system operating at 1.0 T (Siemens Magnetom, Erlangen, Germany) as detailed before. All MRIs were reviewed by the same neuroradiologist (R.M.), who was blinded to the clinical data. The number, location, and size of focal lesions were recorded. Lesions equivalent to the signal characteristics of cerebrospinal fluid on T1-weighted images and measuring more than 3 mm in diameter as well as wedge-shaped cortical-subcortical lesions were regarded as brain infarcts. The size of the lesion was grouped into 4 categories based on the largest diameter (3-9, 10-29, 30-59, and ≥60 mm), and the radii used for calculations were 3, 10, 20, and 30 mm, respectively. The volume of the lesion was estimated using a formula for calculating the volume of a ball.

The sites included lobes (cortical-subcortical lesions in the frontal, parietal, temporal, and occipital lobes), vascular territories (deep and superficial anterior cerebral artery, middle cerebral artery [MCA], and posterior cerebral artery [PCA] areas as well as internal carotid artery), border zone area, and specific locations (putamen, caudate, pallidum, thalamus, genu of internal capsule, anterior and posterior capsule, anterior and posterior corona radiata, anterior and posterior centrum semiovale, and angular gyrus). The thalamocortical connection, which is part of the prefrontal subcortical circuit of Cummings, included the genu, anterior capsule, anterior corona radiata, and anterior centrum semiovale.

RESULTS

Of the 337 patients with ischemic stroke, any dementia was present in 107 (31.8%) and stroke-related dementia in 87 (25.8%). The excluded patients had an older mean age (mean [SD], 73.3 [7.4] years vs 70.2 [7.7] years; P = .002) but did not differ in terms of main demographic and clinical features, including sex, education, and number, side, and site of stroke. The patients with any dementia were older (mean [SD], 71.4 [7.6] vs 69.6 [7.7] years; P = .04) and more often had less than 6 years of education (37.4% vs 23.9%, P = .009) compared with the nondemented subjects.

The total number of infarcts on MRI scans of the 337 patients was 1144. Of the infarcts, 341 (29.8%) were clinically related to the index stroke, 216 (18.9%) were nonrelated, and 587 (51.3%) were silent. Altogether, 587 (51.3%) were silent. Altogether, 548 (47.9%) of the infarcts were located on the left hemisphere and 637 (55.7%) were lacunar. The types (nonlacunar vs lacunar and related vs nonrelated) of infarcts were similar in the patients with and without any poststroke dementia (data not shown).

Mean volumes of the infaracts in the patients with and without any poststroke dementia are detailed in Table 1. The mean total volume of infarcts was 37.7 cm³ in the demented and 22.5 cm³ in the nondemented group (P = .002). Furthermore, the patients with dementia showed larger volumes of all right-sided infarcts, infarcts in any (right- or left-sided) superior MCA and parietal areas, infarcts in right superior MCA and PCA areas, as well as infarcts in the left caudate, anterior capsule, corona radiata, and centrum semiovale. Mean volume of infarcts in the left thalamocortical projection (14.8 vs 4.0 cm³, P = .02) differentiated the 2 groups.

Furthermore, volumes of the related infarcts in the right parietal area (26.4 vs 12.8 cm³, P = .04), in the left anterior capsule (1.8 vs 0.05 cm³, P = .02), and in the left thalamocortical connection (19.0 vs 5.4 cm³, P = .04) were larger in the dementia group.

Mean frequencies of infarcts in the patients with and without dementia are specified in Table 2. The mean total number of infarcts was higher in the dementia group. In addition to the conclusions based on the volumes of infarcts, examining the frequency of infarcts indicated areas where the total infarct volume remained small but the frequency could be critical. These areas included the deep PCA areas as well as the putamen, pallidum, and thalamus, which were affected mainly by lacunar infarcts.

The degree of moderate and severe WMLs and cerebral atrophy is presented in Table 3. The mean Fazekas WML score was higher in the dementia group (3.8 vs 2.9,
The histories of previous and present (index) stroke were reviewed together by a board-certified neurologist (T.P.) and neuroradiologist (R.M.). Infarcts were defined as related or old infarcts. The followings were noted: any moderate or severe central atrophy, any moderate or severe cortical atrophy, and left-sided infarcts separately, all the areas in volume (greatest diameter) and shape into small focal (<3 mm), smooth halo (6-10 mm), and extending cap (>10 mm). White matter lesions along the bodies of lateral ventricles were classified into thin lining (<5 mm), smooth halo (6-10 mm), and irregular halo (>10 mm). White matter lesions in the subcortical, deep, and watershed areas were classified based on size (greatest diameter) and shape into small focal (<3 mm), large focal (6-10 mm), focal confluent (11-25 mm), diffusely confluent (>25 mm), and extensive (diffuse hyperintensity without distinct focal lesions affecting most of the white matter area). The number of each type of WML was counted, and a rating of absent or present was assigned for extensive WMLs. The extent of WMLs was then graded using a 4-point scale based on the methods of Scheltens et al and Erkinjuntti et al. Cortical atrophy and central brain atrophy were rated separately: cortical atrophy in the frontal, parietal, and occipital lobes and in the temporal neocortex, entorhinal cortex (parahippocampal gyrus), and hippocampal formation; and central atrophy in the temporal, frontal, and occipital horns of the lateral ventricles as well as at the bodies of the lateral ventricle. Temporal atrophy was evaluated on 3 coronal slices (the slice showing the interpeduncular cistern and the 2 slices on either side). Medial temporal lobe atrophy included the entorhinal cortex and hippocampus.

The intraobserver and interobserver reliabilities for rating WMLs and atrophy were tested and were found to be good (for white matter changes, weighted κ, 0.72-0.95; for atrophy, weighted κ, 0.61-0.82).

The study was approved by the ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Helsinki, Finland. The study design was first fully explained, and written information was offered to the patients, and if they agreed to participate, a written consent form was signed. In the statistical procedure, we compared the patients with and without DSM-III dementia. The χ² test was applied for categorical data and the pooled t test for continuous data. We analyzed separately the frequencies, mean frequencies, and volumes of all and related lesions. Age, education, and the radiological variables that significantly differentiated the demented and nondemented patients were entered into a multiple logistic regression analysis following 2 different approaches to evaluate the correlates dementia and cognitive impairment: model 1, any dementia, and model 2, stroke-related dementia. No adjustments were made for multiple comparisons in statistical approaches. The statistics were analyzed using the BMDP (Los Angeles, Calif) and SAS (version 6; SAS Institute Inc, Cary, NC) programs.

P<.001). Moderate and severe degrees of atrophy, especially medial temporal lobe atrophy (40.0% vs 19.6%, P<.001), differentiated the 2 groups. In addition, we evaluated a possible association between WMLs and atrophy. The mean WML score was higher in the patients having any moderate or severe cortical atrophy (3.5 vs 2.8, P<.001), medial temporal lobe atrophy (3.9 vs 2.9, P<.001), or any moderate or severe central atrophy (3.6 vs 2.7, P<.001).

Furthermore, we used a logistic regression model to identify the independent correlates of dementia in the whole series. In the first approach (model 1; 337 total patients, 107 demented patients), age, education, the mean frequencies and volumes of all infarcts, right- and left-sided infarcts separately, all the areas in volume described above that significantly differentiated the nondemented from the demented patients in univariate analyses, WMLs as measured by the Fazekas 4-point white matter scale, any moderate or severe central atrophy, and medial temporal lobe atrophy (not present, 0; present, 1) and were included in the model. The following correlates of any poststroke dementia were found (Table 4): medial temporal lobe atrophy (odds ratio [OR], 2.10; 95% confidence interval [CI], 1.10-3.90), WMLs (OR, 1.30; 95% CI, 1.10-1.60), mean frequency of left-sided infarcts (OR, 1.21; 95% CI, 1.01-1.47), volume of the infarct in MCA (OR, 1.11; 95% CI, 1.04-1.20), and education (OR, 0.91; 95% CI, 0.85-0.98). In the second approach (model 2; 306 total patients; 87 demented patients), the focus was stroke-related dementia and the correlates were volume of infarcts in left anterior corona radiata (OR 1.68; 95% CI, 1.12-2.77), WMLs (OR 1.28; 95% CI, 1.10-1.56), volume of infarcts in MCA (OR 1.20; 95% CI, 1.05-1.24), and education (OR 0.92; 95% CI, 0.85-0.98).

The present series is thus far the largest well-defined consecutive series examining MRI correlates of poststroke dementia. The independent correlates of any poststroke dementia in the present series included the combination of infarct features (volume of infarcts in superior MCA and frequency of left-sided infarcts), extent of WMLs, medial temporal lobe atrophy, and host factors (education). The correlates of stroke-related dementia included infarct features (volume of infarcts in right-sided superior MCA and left anterior corona radiata), extent of WMLs, and host factors (education). The increased risk of poststroke dementia associated with most of the quantitative imaging variables, however, was modest.
A larger total volume of infarcts was detected in the dementia group, which accords with a few but deviates from some of the previous studies. The total number of infarcts was also higher in the dementia group, which accords with a few but deviates from some of the previous studies. The total tegic sites in the left hemisphere (thalamocortical connections, putamen, pallidum, and deep PCA areas). Liu et al also reported larger volumes of left-sided infarcts. A higher frequency of infarcts in the left hemisphere was also found in the series reported by Gorelick et al and Figueroa et al. A higher frequency of infarcts in the left hemisphere is further supported by clinical series on post-stroke dementia. A higher frequency of infarcts in the left hemisphere in the total group, but not in the group with stroke-related dementia, suggests the importance of multiple infarcts (old or silent) in the stroke-related dementia group.
The critical role of infarcts involving the thalamocortical connection (including the genu and anterior capsule, anterior corona radiata, and anterior centrum semiovale) is also supported by previous studies showing left anterior capsule infarcts and frontal lesions as independent correlates of poststroke dementia. In the present series, we found the volume of infarcts in the left anterior corona radiata, part of the thalamocortical connection, to be an independent correlate of stroke-related dementia. Also, the seminal case study by Tatemichi et al showed the role of lesions affecting the thalamocortical connection in relation to incident poststroke dementia.

Censori et al, in a series of patients with first-ever stroke, reported more frequent stroke-related dementia. Tatemichi et al, in a nonselected series of poststroke patients, reported more frequent dementia among patients with nonrelated infarcts. We did not find any significant difference in our groups, but the volume of related infarcts in the anterior capsule, thalamocortical connection, parietal lobe, and right hemisphere was larger in the demented than the nondemented patients.

Frequency of infarcts (mainly lacunar) in the deep gray matter (pallidum, putamen, and thalamus), especially on the left side, was higher in the dementia group. This contrasts with some of the previous reports, which did not show a difference.

Extensive WMLs, both in the periventricular and the deep white matter areas, differentiated the demented from nondemented patients in the present series in accordance with some, but not all of the previous studies, which may reflect sample selection, especially in regard to small-vessel disease. Frequency of infarcts in the deep gray matter (56% of all infarcts were lacunae) as well as the extensive WMLs support the idea that small-vessel disease is a major etiopathogenetic factor in poststroke dementia.

Stroke patients are more likely to have WMLs than age-matched controls. White matter lesions are associated with an increased risk of poststroke dementia and indicate a higher risk of stroke recurrence. In the present series, infarcts and WMLs had an independent correlation with poststroke dementia. This accords with the CT series reported by Gorelick et al. The MRI series reported by Liu et al, as well as the community-based clinical CT study reported by Skoog et al.

In previous studies, central atrophy as well as both central and cortical atrophy, have occurred more frequent in patients with poststroke dementia. However, this has not been confirmed by all studies. In the present series, both central and medial temporal lobe atrophy clearly differentiated the demented from the nondemented patients. Medial temporal lobe atrophy was also an independent correlate of any poststroke dementia. Because of strong intercorrelations between atrophy, WMLs, and infarcts, medial temporal lobe atrophy did not reach significant independent correlation with stroke-related dementia in the logistic model. This was also the case in the studies by Gorelick et al and Liu et al. High frequency of medial temporal lobe atrophy may reflect the coexistence of Alzheimer disease but may also be related to delayed ischemic injury in hippocampal areas associated with selective vulnerability.

As a host factor, education was an independent correlate of poststroke dementia in the present study, similar to the findings of Gorelick et al. In our series, the patients with poststroke dementia were also older. Age also has an independent predictor of poststroke dementia in 2 previous series.

Possible study limitations include the following: (1) The present study of hospital-based patients 3 months poststroke may not be representative of community dwelling poststroke patients, because the oldest patients and those with the most severe stroke may not have been admitted to the emergency department of the Helsinki University Central Hospital. Large community-based series could overcome these limitations. (2) There is a lack of neuropathological validation of dementia diagnosis and neuroradiologic findings. (3) Simple ratings of atrophy and WMLs as well as volume estimates of infarcts may be less precise than volumetric methods, especially if groupwise statistical picture analysis could be applied. (4) Multiple statistical comparisons raise the potential problem of showing falsely significant differences. (5) Differences in patient populations studied and definitions of dementia used may limit comparisons with other studies.

In conclusion, this study verifies that correlates of poststroke dementia cannot be represented by a single feature, but rather by a combination of infarct features, extent of WMLs, medial temporal lobe atrophy, and host features.

Accepted for publication January 24, 2000.

This study was supported in part by grants from the Medical Council of the Academy of Finland (Drs Mäntylä, Aronen, and Erkinjuntti); the Clinical Research Institute, Helsinki University Central Hospital (Drs Pohjasvaara and Mäntylä); the Finnish Alzheimer Foundation for Research (Drs Pohjasvaara and Erkinjuntti); and the Paavo Nurmi Foundation (Dr Aronen); and by the Research Grant from the Helsinki University Central Hospital (Dr Aronen) and the University of Helsinki (Dr Erkinjuntti), all in Helsinki, Finland.

We thank Vesa Kusunen, senior research officer, Statistics Finland, Helsinki, for statistical support and review.

Corresponding author: Timo Erkinjuntti, MD, PhD, Department of Clinical Neurosciences, Helsinki University Central Hospital, PO Box 300, FIN-00029 HUHK, Helsinki, Finland (e-mail: timo.erkijn江南@huch.fj).

REFERENCES