Cognitive Decline in Patients with Leukoaraiosis Within 5 Years after Initial Stroke

Emre Kumral, MD,* Halil Güllüoğlu, MD,† Naila Alakbarova, MD,* Emrah E. Deveci, MD,* Ayşe Y. Çolak, MD,* Ayşe D. Çağında, MD,* Dilek Evyapan, MD,* and Mehmet Orman, PhD‡

Background: Leukoaraiosis (LA) is closely associated with cognitive deficits. The association between LA and cognitive disorders, such as mild cognitive impairment (MCI) and dementia, after initial stroke has not been systematically studied. In this study, we sought to identify whether LA contributes to the occurrence of certain type of cognitive disorders after initial stroke. *Methods:* Data from our Stroke Registry were examined, and 5-year follow-up data for LA and cognitive disorders were analyzed. We performed Kaplan–Meier analysis and log-rank test to assess the predictive value of LA for risk of cognitive decline and the Cox proportional hazards model to test the risk factors studied as independent determinants of cognitive impairment. *Results:* The frequency of patients with normal cognitive function decreased significantly at 5 years compared with initial stroke (78% vs 70%; odds ratio, 1.51; 95% confidence interval, 1.41-1.62). Of 8784 patients, 1659 (19%) had dementia and 964 (11%) had MCI at the final analysis. After 5 years of follow-up, survival analysis showed that all patients with LA had an increased probability of MCI compared with those without LA ($P < .0001$). Patients with LA had an increased chance of dementia compared with those without LA ($P < .0001$) at the end of follow-up. Cognitive decline probability was significantly higher in patients with severe LA compared with those with mild/moderate LA ($P < .0001$). Cox regression analyses showed that recurrence of stroke (hazard ratio [HR], 3.92 [95% CI, 3.26-4.72]), hypertension (HR, 1.11 [95% CI, 1.0-1.22]), LA (HR, 1.15 [95% CI, 1.05-1.25]), age (HR, 1.05 [95% CI, 1.04-1.06]), hypercholesterolemia (HR, .86 [95% CI, .77-.95]), higher LDL cholesterol (HR, 1.21 [95% CI, 1.11-1.32]), lower HDL cholesterol (HR, .90 [95% CI, .83-.98]), coronary heart disease (HR, .85 [95% CI, .77-.94]), and National Institutes of Health Stroke Scale score at admission (HR, .77 [95% CI, .72-.82]) were also significantly associated with cognitive impairments. *Conclusions:* Our findings suggest that patients with LA may be at risk of developing new cognitive impairments at long-term period after initial stroke. The evaluation of the concomitant risk factors, besides providing insights about the possible mechanisms behind the cognitive dysfunction present in LA, may be of help for the prevention of cognitive impairments. **Key Words:** Leukoaraiosis—cognitive disorders—mild cognitive impairment—vascular dementia.

From the *Stroke Unit, Neurology Department, School of Medicine, Ege University, İzmir; †Neurology Department, Medical Park Hospital, İzmir University, İzmir; and ‡Biostatistic Department, School of Medicine, Ege University, İzmir, Turkey.

Received March 26, 2015; revision received May 18, 2015; accepted June 14, 2015.

Authors' contributions—Principal author: E.K.; study concept or design: E.K. and H.G.; acquisition of data: N.A., A.Y.Ç., A.D.Ç., and E.E.D.; analysis or interpretation of data: D.E.; statistical analysis: M.O.; and study supervision or co-ordination: E.K. and D.E.

The authors have no actual or potential conflicts of interest for all authors involved in this article.

Ethical committee approval: Ege University Medical Ethical Committee approved this study following the principles outlined in the Declaration of Helsinki before starting the study (1998).

Address correspondence to Emre Kumral, MD, Faculty of Medicine, Stroke Unit, Department of Neurology, Ege University, Bornova, İzmir 35100, Turkey. E-mail: emre.kumral@ege.edu.tr.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.06.012

Introduction

Leukoaraiosis (LA) is a major risk factor contributing to the causes of stroke patients. LA is an independent predictor of stroke,[1] hemorrhagic transformation after thrombolysis for ischemic stroke,[2] stroke recurrence,[3] and poststroke dementia.[4,5] Significant LA progression is seen in elderly individuals who present with moderate-to-severe white matter changes irrespective of clinical symptoms.[6] Early studies reported conflicting results about the relationship between LA and the cognitive decline probably attributable to heterogeneity of stroke and cognitive impairments with variable pathogenesis.[6-8] Nowadays, it is well known that there is a strong association between LA and cognitive dysfunction.[9,10] The presence of LA may facilitate occurrence of new cognitive deficits after an initial stroke. Recent studies including patients with burden of LA supports the clinical relevance of these brain abnormalities because subjects with severe white matter changes had worse global cognitive performance and showed rapid functional decline as early as after the first year of follow-up in comparison with those individuals with only mild LA at baseline.[11,12]

In the present study, we sought to determine whether LA play a role in long-term period on the cognitive status of patients after initial stroke. By our data analysis, a relationship between LA and risk of cognitive decline could have both biologic and clinical implications, offering insights into the pathophysiological mechanisms of vascular cognitive disorders.

Materials and Methods

The enrollment of patients in this study was started in January 1998 and stopped in January 2009. Detailed baseline data were abstracted prospectively using paper-based registry forms and stored in the computer environment. All patients with stroke having cerebrovascular risk were recruited from the outpatient clinic of the Department of Neurology, Ege University Medical Center (Izmir, Turkey). The methods of case ascertainment and data gathering in the Ege Stroke Registry were described as published elsewhere.[13] The objectives of the Ege Stroke Registry were to determine the risk factors in patients presenting with a manifestation of cerebrovascular disease and cognitive deficits to study predictors for future cardiovascular and cerebrovascular events and cognitive impairments in these high-risk patients. Prospectively recorded variables included age, gender, risk factors, blood pressure, and National Institutes of Health Stroke Scale (NIHSS) score at the time of admission, clinical and etiological subtypes, topography of infarcts on magnetic resonance imaging studies (T1, T2, and fluid-attenuated inversion recovery [FLAIR] sequences), cardiovascular tests including electrocardiography and echocardiography, inhospital recurrent stroke, neurologic and systemic complications, and modified Rankin Scale score at the time of discharge.

Patients were followed up for 6 months and then annually in 5 years by a visit to determine whether they had new cognitive symptoms or neurologic deficit. The study was approved by the ethics committee of the Ege University Medical Center, and written informed consent was obtained from all participants.

LA Definition and Measure

LA was identified by the presence of any white matter hypodensity within the region starting at the lateral ventricular border and extending up to the corticomedullary junction on magnetic resonance imaging and/or increased signal intensity on acute T2 and FLAIR images unlike the sharply defined low-density lesions within a specific arterial territory. Hyperintense lesions involving the convolutional white matter, U-fibers, corpus callosum, internal capsule, and anterior commissure were not regarded as LA. Also excluded from LA outlines were chronic infarcts that clearly corresponded to a vascular territory according to previously published templates.[14] The Fazekas Visual Scale[15] was used for quick assessment of LA severity on T2 and FLAIR images. Fazekas scores were stratified into 2 groups: mild/moderate LA (Fazekas score 0-2) and severe LA (Fazekas score 3). If we did not identify any white matter hyperintensity, we recorded as absent.

All magnetic resonance imaging measurements were performed by readers blinded to clinical data, including clinical outcome. All LA ratings were done by 2 neuroradiologists blinded to cognitive status. The [kappa] coefficient for lesion outlining was reported to be .99 for FLAIR and diffusion-weighted imaging for LA extension in a set of 150 consecutive patients.

Stroke Subtypes

Subtype classification of stroke was based on patient's clinical features combined with the results of 1 or more diagnostic tests.[13] Large-artery disease (LAD), small-artery disease (SAD), cardioembolism, and other determined and undetermined causes stroke were defined according to previously published criteria.[16] Spontaneous, nontraumatic intracerebral hemorrhage (ICH) was diagnosed by computed tomography or magnetic resonance imaging. Localization of intracerebral hemorrhage was also recorded in our data system.

Diagnosis of Dementia and Cognitive Decline

The diagnosis of dementia was determined according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[17] and the International Workshop of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et