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Cognitive impairment one year after ischemic stroke: predictors and dynamics of significant determinants

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Background/aim: Evidence suggests that the risk for dementia increases after stroke. This study investigated the dynamics of the neurological and cognitive status of patients with no baseline dementia over a 1-year period after ischemic stroke.

Materials and methods: We examined 47 ischemic stroke patients admitted within 48 h of ictus. Their neurological and cognitive statuses, blood biochemical parameters, and microalbuminuria levels were prospectively evaluated over a 1-year period post-stroke.

Results: A more severe neurological deficit was found in the cognitively impaired patients (P = 0.003). The NIHSS score over a 1-year follow-up period improved only in patients with normal cognition (P = 0.000). Time-varying dynamics of the MMSE score were observed in both patient groups (P = 0.000). Age (P = 0.000), education (P = 0.004), sex (P = 0.041), history of diabetes (P = 0.045), and serum high sensitive C-reactive protein (hs-CRP) on admission (P = 0.003) were significant determinants of cognitive decline 1 year after a stroke. The albumin-to-creatinine ratio was high during the whole follow-up period in the cognitively impaired group after adjusting for sex and age (P = 0.010). Binary logistic regression showed that hs-CRP (P = 0.013) and age (P = 0.010) were independent predictors of patients' cognitive status 1 year after stroke.

Conclusion: The level of inflammatory markers could be considered as an additional criterion of long-term cognitive impairment.

Key words: Cognitive impairment, hs-CRP, ischemic stroke, long-term prognosis, endothelial dysfunction

1. Introduction

Stroke survivors display a variety of disabling symptoms such as motor deficit, sensory disorders, and aphasia that have been widely discussed in the medical literature. Limited studies have focused on poststroke cognitive dysfunctions (1,2). Although patients may physically fully recover after a stroke, they often remain unable to live independently due to poor cognitive status. Even patients with only mild poststroke cognitive deficits can have substantial disability and are at an increased risk of cognitive deterioration. Untouched opportunities still exist for prevention and treatment.

The reported incidence of cognitive decline within the first month after stroke varies significantly depending on the definition of deficit and the patient selection criteria. Despite the ability of the brain to compensate for tissue impairment, which can result in cognitive improvement, most patients show little progress and develop long-term cognitive deterioration. The poststroke cognitive decline mechanisms in the chronic phase of cerebral ischemia are still insufficiently investigated.

Research shows that stroke increases the risk for cognitive impairment regardless of demographic and vascular risk factors (3,4). An association exists between cognitive dysfunction and lesion localization (5). Factors such as stroke characteristics (dysphasia and dominant syndromes) and previous vascular events independently increase the risk for cognitive injury (2). Some vascular risk factors, including history of diabetes, hypertension, and TIA, are also closely related to cognitive deterioration in the subacute and chronic phases of stroke (6). The importance of these factors stems from the fact that they predispose to cognitive decline even in the absence of a previous stroke.

The role of inflammatory mechanisms and endothelial dysfunction in poststroke cognitive impairments has not been extensively studied (6). Limited data have shown that elevated levels of some inflammatory markers in the circulation of ischemic stroke patients imply a lower grade of poststroke global cognition (7).

The present study was performed in an attempt to examine:

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- The dynamics of the neurological and cognitive status of patients with no baseline dementia over a 1-year period after ischemic stroke.
- The dynamics of peripheral leukocytes, lipid profile components, and microalbuminuria over a 1-year period after ischemic stroke and the difference in these parameters between cognitively normal and cognitively impaired patients.
- Independent predictors of cognitive decline in the first year following stroke.

2. Materials and methods

2.1. Study population

Out of 63 ischemic stroke patients admitted to the Department of Neurology, University Hospital in Pleven, Bulgaria, from October 2006 through April 2009, we selected 47 (26 men and 21 women). The study did not include individuals with a history of acute or chronic infection, cancer, kidney or liver disease, or preceding surgical intervention. Additional exclusion criteria were the presence of subarachnoid or intracerebral hemorrhage, the absence of a CT scan of the brain at admission, prestroke dementia, and neurological or psychiatric disorders that can cause cognitive dysfunction. The patients were screened for depression using the Hamilton Depression Rating Scale (8), and those with depression were also excluded from the study.

A detailed questionnaire assessing the medical history and physical state of the patients was filled out by an experienced neurologist. Arterial hypertension was defined as mean systolic pressure >140 mmHg and mean diastolic pressure >90 mmHg. Diabetes mellitus was defined as a blood glucose level of >7.1 mmol/L.

All experiments were conducted in accordance with the rules and regulations approved by the University Research Ethics Committee.

2.2. Neurological examination

National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) scores were used to determine the neurological deficit and clinical outcome, respectively, at discharge and at 3, 6, and 12 months following the stroke. Cognitive status was evaluated by the Mini Mental State Examination (MMSE) score (the maximum score of the MMSE can be 30 points; a lower score is an indication of impaired cognition). For repeated measure analysis and binary logistic regression, the cognitive status in the first year after stroke was represented by a dichotomous variable indicating "normal cognition" (coded 0) if the MMSE score was ≥24 points or "cognitive deficit" (coded 1) if the MMSE score was <24 points.

2.3. Biochemical tests

Peripheral venous blood and morning spot- and 24-h urine samples were collected at admission and at 3, 6, and 12 months after stroke. Blood biochemistry was studied using standard methods. The collected sera were stored at –20 °C until assayed. The serum level of high sensitive C-reactive protein (hs-CRP) was measured by a turbidimetric method on admission (9). Urinary albumin and creatinine were measured using the Cobas Integra system (Roche Diagnostics). Urinary albumin was measured by the immunoturbidimetric method. Urinary creatinine was measured by the kinetic Jaffe reaction (10).

2.4. Statistical analysis

Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square or Fisher exact tests were used to compare proportions between patient groups. The interval variables were represented as mean (±standard deviation) or median (25th–75th percentile), depending on the type of distribution.

Normality of distribution was checked with the Shapiro–Wilk test. The significance of differences between groups was assessed using the Student t-test and one-way ANOVA for normally distributed data, along with the Mann–Whitney U test and the Kruskal–Wallis test for nonparametric data. Spearman or Pearson product moment correlations were used to examine the relationships between clinical and biochemical parameters.

Two approaches were applied to study the dynamics of neurological and cognitive status and the biochemical parameters over the 1-year poststroke period. For normally distributed data, general linear model repeated measures analysis with the univariate test of within-subjects effects was used. In the case of violation of the sphericity assumption, the adjusted P-values given by the Greenhouse–Geisser correction were applied. Bonferroni correction for multiple comparisons was made for P-values. For nonparametric data, the Friedman test was carried out. Post hoc analysis with Wilcoxon signed-rank tests was conducted with Bonferroni correction, resulting in a significance level set at $P < 0.0083$ (for 4 levels and 6 pairwise comparisons). A log transformation was applied to obtain normal distribution of data in most cases.

A binary logistic regression model was built to assess the predictive value of statistically significant factors on the dichotomous dependent variable "cognitive status 1 year after stroke". The calibration of the model, or the extent to which the observed and predicted probabilities matched, was evaluated by a Hosmer–Lemeshow goodness-of-fit test. The discrimination ability of the model, i.e. the capacity to differentiate patients with cognitive impairment from those with normal cognition, was assessed with receiver operating characteristic (ROC) curve analysis by calculating the area below the ROC curves. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Basic characteristics of the study population

The basic characteristics of the study population and the potential factors affecting cognition in the first year after stroke are given in Table 1. Twenty-six (55%) of the 47 patients were males. The age of the participants varied from 56 to 76 years (median: 63). Localization of the infarction was as follows: left hemisphere - 21 patients (frontal -9; parietal - 8; thalamic - 1; capsular - 3); right hemisphere - 21 patients (frontal - 8; parietal - 4; thalamic - 3; capsular - 6), and stem - 5 patients. Forty-three percent of the patients showed mild to moderate cognitive impairment, and 34% were at risk for developing cognitive deficit 1 year after stroke.

Age, sex, level of education, history of diabetes, WBC count in the first year after stroke, and serum hs-CRP level at hospital admission were significant factors for cognitive deterioration 1 year after stroke (Table 1).

3.2. Dynamics of neurological and cognitive status

Significant time variations in the NIHSS scores over a 1-year period were found in the cognitively intact patients ($\chi^2(3) = 23.071$, $P = 0.000$) (Figure 1A). Furthermore, their neurological statuses gradually improved, and a significant difference was reached between the admission scores and the third-month scores ($Z = -2.900$, $P = 0.004$), and between the admission scores and the 1-year scores ($Z = -2.641$, $P = 0.008$). No significant time variations in the NIHSS scores over a 1-year period were found for the cognitively impaired group ($\chi^2(3) = 0.931$, $P = 0.818$). The neurological deficit severity was higher in the cognitively impaired than in the cognitively normal subjects ($\chi^2(3) = 13.748$, $P = 0.003$). Time-varying dynamics of the MMSE score were observed in both the cognitively normal ($\chi^2(3) = 25.358$, $P = 0.000$) and cognitively impaired ($\chi^2(3) = 45.816$, $P = 0.000$) groups (Figure 1B). Cognition deteriorated within a 3-month period in patients who remained cognitively intact at 1 year post stroke (discharge/3rd month, $Z = -3.598$, $P = 0.000$). Cognition deteriorated within 6 months in the cognitively impaired patients and became stationary afterwards (discharge/3rd month, $Z = -3.571$, $P = 0.000$; and 3rd month/6th month, $Z = -2.953$, $P = 0.003$).

3.3. Dynamics of peripheral leukocyte count, lipid profile components, and microalbuminuria

A temporal profile of WBC count towards reduction was found for both cognitively normal ($\chi^2(3) = 20.309$, $P = 0.000$) and cognitively impaired ($\chi^2(3) = 10.484$, $P = 0.015$) patients (Figure 1C). A difference between separate points in time was established only for the cognitively normal group (admission/3rd month, $Z = -2.646$, $P = 0.008$; 3rd month/6th month, $Z = -2.823$, $P = 0.005$; 6th month/1st year, $Z = -2.796$, $P = 0.005$; and admission/1st year, $Z = -3.354$, $P = 0.001$). The WBC count was higher in the cognitively impaired as compared with the cognitively intact group within the whole 1-year period ($\chi^2(1) = 6.167$, $P = 0.013$).

The granulocytes were the only cells responsible for the observed difference in the WBC count between the two patient groups since statistical significance was reached only for them (inset in Figure 1C). The Greenhouse–Geisser test did not show any time dependence in the granulocyte count ($F = 2.919$, $P = 0.078$) in either group. The granulocyte count was persistently higher in the cognitively impaired than in the cognitively intact patients ($F = 8.205$, $P = 0.006$). The difference remained significant after adjusting for sex and age ($F = 7.042$, $P = 0.011$).

No significant time variations and differences were found between the groups in the lipid profile components (total cholesterol, LDL, HDL, TG, LDL/HDL, and cholesterol/HDL). The albumin-to-creatinine ratio was higher in the cognitively impaired group ($F = 7.134$, $P = 0.010$), and the difference remained significant after adjusting for sex and age ($F = 4.408$, $P = 0.042$) (Figure 1D). No significant time variations were observed in either group ($F = 2.525$, $P = 0.117$).

3.4. Independent predictors of cognitive decline at 1 year after stroke

We created a binary logistic regression model to identify the independent predictors of the 1-year cognitive decline. The cognitive status in the model was represented as a dichotomous outcome variable. The explanatory variables included two demographic factors (sex and age), an inflammatory marker (hs-CRP), and a vascular risk factor (history of diabetes), thus meeting the requirement for the ratio of the number of events per variable to be greater than 10.

Education was excluded from the model because of an insufficient number of cases observed in some subgroups. The WBC count measured in the first year post stroke was also excluded since an inflammatory marker had already been introduced in the model.

The existence of a relationship between the dichotomous outcome variable and the combination of independent variables was confirmed by the statistical significance of the block chi-square ($\chi^2 = 31.009$, $P = 0.000$). Wald statistics showed that age ($P = 0.010$) and hs-CRP ($P = 0.013$) were significant predictors of cognitive decline (Table 2). Furthermore, an increase by 1 year in age and by 1 mg/L in hs-CRP resulted in a 30.9% and 18.9% increase in odds of cognitive decline in the first year after stroke, respectively. Nagelkerke R^2 analysis showed that about 65% of the variation in the cognitive status could be explained by this logistic model. The Hosmer–Lemeshow goodness-of-fit measure confirmed that the entire model matched the observed values ($\chi^2 = 2.777$, $P = 0.905$). The area under the ROC curve, used to assess the model's

Table 1. Characteristics and potential factors associated with cognitive status 1 year after stroke.

Parameters	All patients (n = 47)		Cognitive status 1 year post stroke						
			Normal (n = 11)		Risk of deficit (n = 16)		Mild to moderate deficit (n = 20)		P-value
Age [years], median (25th–75th)	63	(59–69)	58	(57–59)	64	(60–69)	67	(63–71)	0.000*
Male sex, n (%)	26	(55)	9	(81)	10	(63)	7	(35)	0.041*
Education, n (%)									0.004*
8th grade	9	(19)	0	(0)	3	(19)	6	(30)	
High school	24	(51)	3	(27)	8	(50)	13	(65)	
College	5	(11)	4	(36)	1	(6)	0	(0)	
University	9	(19)	4	(36)	4	(81)	1	(5)	
Vascular risk factors									
Arterial hypertension, n (%)	45	(96)	9	(82)	16	(100)	20	(100)	0.051
Systolic blood pressure [mmHg], (SD)	158	(29)	143	(28)	161	(23)	164	(33)	0.150
Diastolic blood pressure [mmHg], (SD)	95	(16)	90	(13)	95	(19)	97	(15)	0.603
Diabetes mellitus, n (%)	13	(28)	0	(0)	6	(38)	7	(35)	0.045*
Alcohol abuse, n (%)	10	(21)	4	(36)	2	(13)	4	(20)	0.308
Cigarette smoking, n (%)	19	(40)	6	(54)	7	(44)	6	(30)	0.379
History of stroke, n (%)	10	(21)	3	(27)	3	(19)	4	(20)	0.814
Neurological examination									
NIHSS score [1*], median (25th–75th)	5	(4–6)	5	(2–7)	4	(3–5)	5	(4–7)	0.130
NIHSS score [2], median (25th–75th)	3	(2–5)	2	(0–3)	2	(1–4)	3	(2–12)	0.035*
mRS score [1*], median (25th–75th)	1	(1–2)	1	(1–2)	1	(1–2)	2	(1–2)	0.463
mRS score [2], median (25th–75th)	1	(1–2)	1	(0–1)	1	(0–1)	1	(1–3)	0.180
Radiological variables									
Localization, n (%)									0.126
Hemispherical	39	(83)	8	(73)	13	(81)	18	(90)	
Lacunar	3	(6)	0	(0)	1	(6)	2	(10)	
Stem	5	(11)	3	(27)	2	(13)	0	(0)	
Biochemistry									
WBC[1] [$\times 10^9$/L], (SD)	7.8	(1.7)	7.0	(1.3)	7.7	(1.3)	8.3	(2.1)	0.154
WBC[2] [$\times 10^9$/L], (SD)	7.6	(1.9)	6.6	(1.4)	7.3	(1.5)	8.3	(7.7)	0.043*
Glucose[1] [mmol/L], median (25th–75th)	5.5	(5.1–6.8)	5.2	(4.7–5.5)	6.3	(5.3–7.2)	5.5	(5.2–6.8)	0.093
Glucose[2] [mmol/L], median (25th–75th)	5.6	(5.4–6.6)	5.8	(5.5–6.3)	5.6	(5.3–7.0)	5.7	(5.4–6.7)	0.857
Cholesterol[1] [mmol/L], median (25th–75th)	5.1	(4.5–5.6)	5.0	(4.4–5.5)	4.7	(4.4–5.2)	4.9	(4.7–5.6)	0.226
Cholesterol[2] [mmol/L], median (25th –75th)	5.1	(4.5–5.8)	5.1	(4.5–5.9)	4.9	(4.7–5.6)	5.2	(4.5–6.1)	0.964
TG[1] [mmol/L], median (25th –75th)	1.7	(1.3–2.0)	1.6	(1.2–2.1)	1.5	(1.3–2.1)	1.7	(1.3–2.0)	0.865
TG[2] [mmol/L], median (25th –75th)	1.4	(1.4–2.0)	1.7	(1.0–1.7)	1.3	(1.0–1.8)	1.9	(1.2–2.6)	0.087
hs-CRP[1] [mg/L], median (25th –75th)	2.6	(1.4–14.6)	1.9	(1.2–2.5)	1.8	(0.7–7.2)	12	(4.3–35)	0.003*
ACR[1] [mg/mmol], median (25th –75th)	0.8	(0.5–1.6)	0.7	(0.4–1.3)	0.7	(0.4–1.3)	1.3	(0.6–2.7)	0.143
ACR[2] [mg/mmol], median (25th –75th)	1.1	(0.5–3.6)	0.8	(0.4–1.3)	1.0	(0.4–2.6)	2.1	(0.7–6.7)	0.186

[1] at admission; [1*] at discharge; [2] 1 year post stroke.
ACR – Albumin-to-creatinine ratio, hs-CRP – high sensitive C-reactive protein, mRS – modified Rankin Scale, n – number of patients, NIHSS – National Institutes of Health Stroke Scale, SD – standard deviation, TG – triglycerides, WBC – white blood cells.

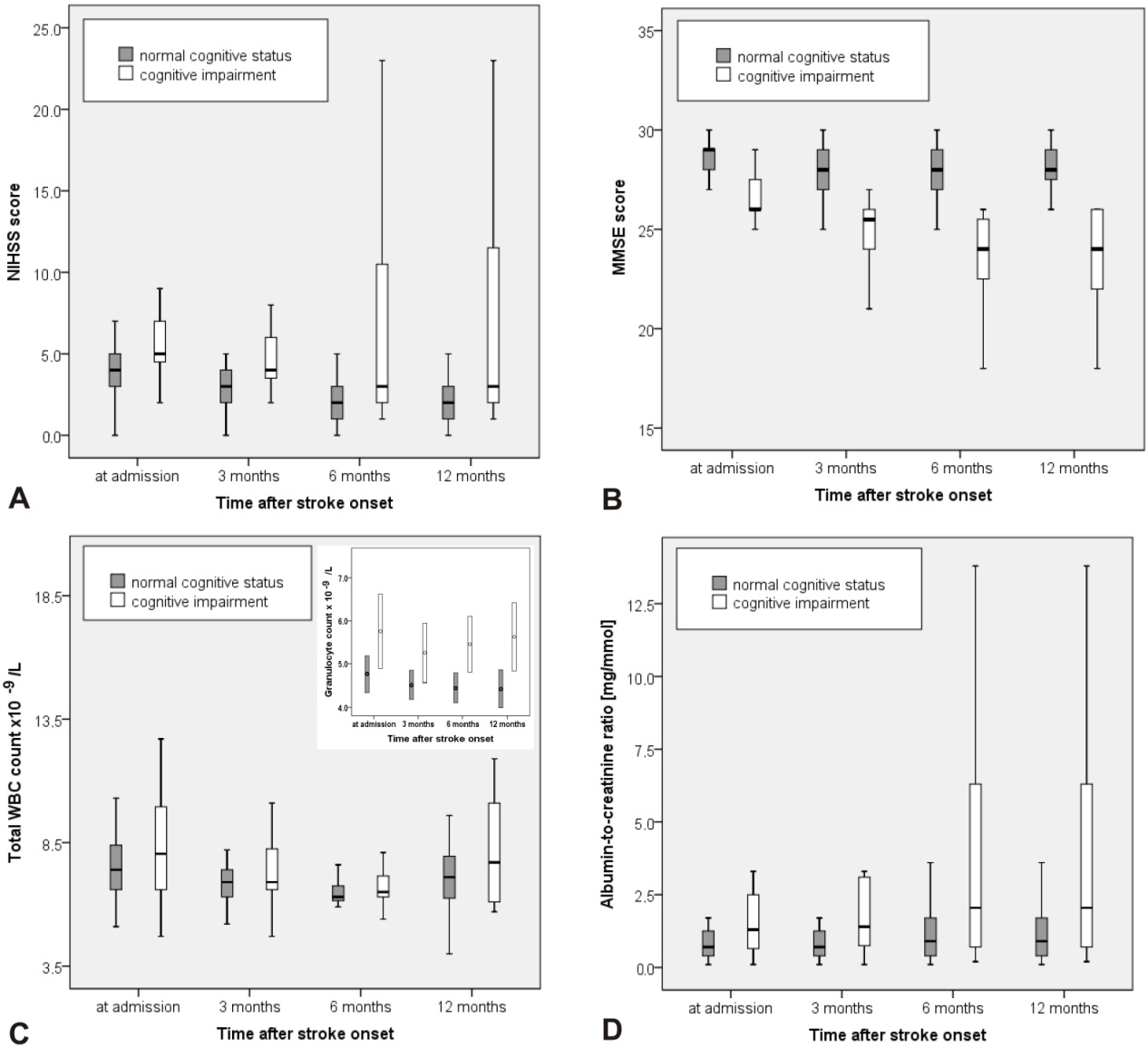

Figure 1. A temporal profile of neurological and cognitive status and significant biochemical parameters over a 1-year poststroke period. Data are given as mean (±SD) or median (minimum–maximum values).

discrimination ability, was 0.906 (0.827–0.986), which meant that in almost 91% of all possible pairs of patients in which one had a normal cognitive status and the other had a cognitive impairment, the model would assign a higher probability to the patient with cognitive impairment. The optimal sensitivity found was 75% and the specificity was 84%.

4. Discussion

Cognitive impairments are often seen after a stroke (1,2,11). About half of the ischemic stroke patients included in the present study who had not had prestroke dementia and had no poststroke depression developed mild to moderate cognitive deficit in the first year after the stroke. Similar results were reported by Serrano et al. (11). Other researchers also reached the conclusion that a cerebrovascular event may have a major detrimental effect on cognition even in patients with a low baseline risk of dementia (3).

The objective of the present study was to establish important determinants of cognitive deficit that can be evaluated immediately after stroke onset and may prove useful in predicting cognitive decline in the first year after the stroke. In addition, our aim was to follow up on the dynamics of some biochemical parameters over a 1-year poststroke period to determine whether there is any

Table 2. Logistic regression model of factors predicting cognitive decline in the first year after stroke.

Variables	B	S.E.	Wald	d.f.	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Age [years]	0.270	0.105	6.602	1	0.010	1.309	1.066	1.608
Sex	1.325	0.888	2.226	1	0.136	3.761	0.660	21.428
History of diabetes	–0.209	0.917	0.052	1	0.819	0.811	0.135	4.891
hs-CRP [mg/L]	0.173	0.070	6.210	1	0.013	1.189	1.038	1.363
Constant	–19.679	7.202	7.467	1	0.006	0.000		

hsCRP – High sensitive C-reactive protein, d.f. – degrees of freedom, Exp(B) – odds ratio, S.E. – standard error, Sig. – significance, CI – confidence interval.
Cognitive status: normal [MMSE = 0], cognitive impairment [MMSE = 1]. Sex: male = 1, female = 2. History of diabetes: yes = 1, no = 2.

difference in their values found in cognitively impaired and cognitively intact patients.

Our results demonstrated that the patients who developed mild to moderate cognitive impairment were advanced in age and predominantly females, with low levels of education, a history of diabetes, and high serum hs-CRP levels on admission. Moreover, patients who developed cognitive deterioration had a more active immune status than those who remained cognitively normal, resulting in higher WBC and granulocyte counts over the 1-year poststroke period. Among the significant determinants, serum hs-CRP and age were the only independent predictors of cognitive decline 1 year after a stroke.

In our study, the effect of lesion localization on the cognitive status 1 year after a stroke was not significant. This could be attributed to the fact that most of the patients (83%) had hemispheric infarctions. The relationship between lesion localization and long-term cognitive decline is worth attention in future research.

A distinctive feature of inflammatory reaction in the brain is the activation of resident microglia accompanied by the recruitment and infiltration of peripheral inflammatory cells. The activation of inflammatory cells is known to stimulate the production of proinflammatory factors that in turn stimulate the liver synthesis of CRP (12). Such conclusions were supported by the correlations that we established between the serum hs-CRP levels and the WBC (Rs = 0.301, P = 0.040) and granulocyte (Rs = 0.389, P = 0.007) counts on admission. On the other hand, microalbuminuria, a marker of endothelial dysfunction of the kidneys or brain vessels, is thought to be caused by oxidative processes and inflammation. Some data published in the literature have indicated an association between albuminuria, markers of inflammation, and cognitive decline. We also found a positive correlation between the hs-CRP levels and the albumin-to-creatinine ratio within the first 48 h of stroke onset (Rs = 0.465, P = 0.001). Moreover, this ratio remained high in the cognitively impaired group during the whole follow-up period even after adjustment for sex and age. The finding also suggests the existence of persistent endothelial dysfunction in the cognitively impaired subjects. Our results demonstrated that stroke-induced acute inflammation was the major cause of long-term cognitive deterioration since the relationship between hs-CRP levels and cognition was independent of the vascular risk profile of the patients.

Postischemic inflammation is a dynamic process comprising a complex network of different interactions that develop against the background of concomitant vascular risk factors. The risk factors themselves also contribute to cognitive impairment, and their effect could be mediated by low-grade chronic inflammation.

Age was found to be an independent predictor of cognitive decline in the first poststroke year. This finding is in accordance with previous studies, which have established that age predicts poststroke cognitive dysfunction (13,14). A variety of age-related functional changes in the brain may reduce its capacity to compensate for stroke-initiated vascular injury (15). On the other hand, aging itself is normally accompanied by memory impairment (16). A likely cause of age-related cognitive decline could be the degenerative processes in the brain that develop against a background of chronic subclinical inflammation (17). Indeed, enhanced serum hs-CRP levels are associated with cognitive deterioration in the elderly without a history of cerebrovascular events (18). The results of our study show that the combined effect of factors such as aging and inflammation could significantly increase the susceptibility of the brain to further cerebral damage after stroke. Aging, with its accompanying chronic inflammation, and infarction, which initiates acute inflammation, have

similar vascular pathophysiologies. Together they possibly exert additive effects on cognitive decline.

We found that the level of education, sex, and history of diabetes mellitus were significant determinants of cognitive decline 1 year after stroke, as shown in previous studies (13,14). However, these did not emerge as independent predictors of long-term cognitive status. Generally, a low education level is associated with decreased functional cognitive reserve, and it also may have an impact on lifestyle and risk factor profile. On the other hand, the women in the study were more likely to have cognitive impairment 1 year after the stroke, which is consistent with data previously published (19). A likely explanation of this observation is the fact that the immune system of elderly women is more active than that of men of the same age, as judged by the levels of some cytokines in the circulation (17). Our data indicated that a history of diabetes correlated with both the functional and the cognitive outcome in patients ($\chi^2 = 9.265$, $P = 0.05$). Previous studies have even identified diabetes as an independent predictor of poststroke dementia, which could not be confirmed in this study. Obviously, some factors such as inflammation and diabetes are strongly interdependent. Other stroke risk factors, including alcohol abuse, smoking, and a previous stroke, were not found to influence the poststroke cognitive status, but these could increase the risk for cognitive deterioration by increasing the risk of stroke.

The present study has several limitations. 1) Although the MMSE is currently the most widely used cognitive screening instrument, it has some weaknesses. A detailed neuropsychological battery of tests may allow examining the effect of stroke on a number of cognitive functions. 2) Although the established predictive model was validated using ROC analysis, the results are limited by the small sample size. 3) Another limitation is that the parameters of inflammation and endothelial dysfunction were measured in the circulation, and these do not necessarily reflect local brain processes.

In conclusion, we established that age and serum levels of hs-CRP in the acute phase of stroke were independent predictors of cognitive deterioration in the first year after a stroke. Furthermore, patients who developed cognitive deterioration demonstrated reactive immune statuses and endothelial dysfunction. Together, aging and inflammation may have the potential to increase brain susceptibility to long-term cognitive impairment after stroke. The role of inflammation in poststroke cognitive impairment needs to be further explored in large-scale prospective studies.

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