Evaluation of the coexistence of cognitive disorders, leukoaraiosis and other risk factors in patients with stroke

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Abstract

Background. Stroke is a common cause of mortality and disability. There are many risk factors for stroke among which leukoaraiosis (LA) is mentioned. Historically, LA was a radiological term, however, today it is classified as Cerebral Small Vessel Disease (CSVD) which clinical presentation depends on the affected brain area. Higher prevalence of LA is found not only in stroke patients, but also in patients with hypertension and other cerebrovascular risk factors. Therefore, the aim of the study was to evaluate the relationship between the present LA, selected laboratory tests, the carotid ultrasound markers and cognitive tests results in patients with stroke.

Material and methods. The study included 102 patients (W: 56, M: 46) at the age of 70.9 ± 11.5 hospitalized due to stroke in the Stroke Unit of the Department of Neurology. The clinical assessment included NIHSS score, MMSE testing, laboratory blood tests, carotid duplex USG and CT scan of the brain. Patients were dichotomized based on the presence of LA in the CT scan.

Results. LA was present in 25 (24.5%) patients. It was more frequently found in older patients (>72 years old; $p < 0.001$). In the LA group, higher levels of LDL cholesterol ($p = 0.002$), lower hemoglobin concentration ($p = 0.03$) and higher platelets count ($p = 0.04$) were observed. The carotid ultrasound showed higher intima-media complexes in the LA group ($p = 0.02$). The functional test showed lower scores on the clock test in patients with LA ($p = 0.04$). The presence of LA was three times less likely to be present in patients administered with beta1-adrenolytics ($p = 0.03$).

Conclusions. The occurrence of leukoaraiosis in patients with acute stroke is associated with clustering of other vascular risk factors cognitive impairment, and may be related to ongoing cardiovascular therapy.

Key words: stroke; leukoaraiosis; Doppler ultrasound; beta1-adrenolytics; clock test

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Introduction

Every two seconds someone in the world suffers from a stroke, causing serious consequences and affecting daily routines and quality of life [1]. Annually, 6 million people worldwide die as a result of a stroke, which constitutes the third most common cause of

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death following myocardial infarctions and tumors [2]. Furthermore, among people over 45 years old, stroke is the most common cause of disability. However, these are not the only consequences of stroke. Another complex problem related to strokes arises from cognitive dysfunction which, alongside neurological impairment, influences financial, social and emotional aspects of the patients [2, 3]. Many studies have confirmed that even a minor stroke affects everyday routine, executive, cognitive or neurological functions, what may contribute to difficulty in returning to work and as a consequence reduce patients' quality of life. [4]

Healthcare and treatment methods are becoming increasingly better, which prolongs life expectancy and significantly reduces patients' mortality. However, there are increasing numbers of disabled stroke patients, who require long-term care, rehabilitation and more frequent hospitalizations. That and many other factors have resulted in a continuous increase in financial expenditure on the health care system [2, 5]. Numerous studies have documented that stroke risk factors control and early treatment strategies introduction are efficacious in primary and secondary prevention. Among the risk factor, the most important are: poor hypertension control, dyslipidemia, ischemic heart disease, arrhythmia, atherosclerosis, the presence of leukoaraiosis and lack of physical activity [6, 7].

After many years, Leukoaraiosis (LA) has not only become a radiological term, but also a complex clinical syndrome, the symptoms and pathogenesis of which have not yet been fully described [8, 9]. LA is currently classified as Cerebral Small Vessel Disease (CSVD) which is based on a chronic ischemia resulting from changes occurring in the small arteries of the brain [10]. In Computed Tomography (CT) examination, it occurs in the form of hypodense changes, with varying degrees of density reduction compared to the normal white matter. In magnetic resonance imaging (MRI) in T2-dependent images and FLAIR (fluid-attenuated inversion recovery) sequences, it appears as hyperintensive changes in relation to the normal white matter. LA is mainly located bilaterally in the periventricular regions [11].

Compared to a healthy population, a higher prevalence of LA is found not only in stroke patients but is also in patients with hypertension and other cerebrovascular risk factors [6, 7]. Many studies revealed that not only does leukoaraiosis escalate the risk of stroke but it also affects the severity and worsens the prognosis (Modified Rankin Scale; mRS) [12]. It was also shown that the presence of leukoaraiosis is associated with an increase in patients' mortality due to cardiovascular factors [13].

As the pathogenesis of LA is yet to be elucidated, the aim of our study was to prospectively evaluate the relationship between the occurrence of LA, lipid parameters, carotid and vertebral arteries Doppler ultrasound results, and the presence of the cognitive disorders in patient with a newly diagnosed stroke.

Material and Methods

Study Population

The presented study is a retrospective analysis of the data of patients with stroke hospitalized in the Stroke Unit of the Neurology Department in Zabrze, Medical University of Silesia. All data was obtained from the medical history of patients. The research group comprised 102 patients, including 56 women and 46 men. The average age in the study population was 70.9 ± 11.5 years (mean ± SD) . Patients with defective awareness or aphasia were disqualified from the research due to the deficit of cognitive functions and they have not been taken into account in the total number of respondents. Every single patient was submitted to physical examination, neurological examination with the National Institutes of Health Stroke Scale (NIHSS) evaluation upon admission to the ward. In order to assess cognitive dysfunctions, the Mini-Mental State Examination (MMSE) test was performed, the results of which were adapted for the age and period spent in education, as well as, the clock drawing test (CDT). All patients underwent computed tomography (CT) examination of the brain, total cholesterol, LDL, HDL, triglycerides, as well as, carotid duplex ultrasonography with an assessment of intima-media thickness in the common carotid artery (CIMT — carotid intima-media thickness). CIMT measurements were performed on the distal wall of each of the common carotid arteries. The average value from three measurements carried out on each side was taken into account. Based on CT results, patients were divided into two subgroups: patients with leukoaraiosis (GSL test group with leukoaraiosis, n = 25) and those, where leukoaraiosis was not detected (GC control group, n = 77).

Ethics

All clinical and demographic data, as well as, outcome information were obtained retrospectively from the patients' medical records. At the time of hospitalization, patients consented to all diagnostic

and treatment procedures which were pursuant to the guidelines appropriate for stroke. All procedures were performed in accordance with the Declaration of Helsinki on the treatment of human subjects.

Statistical analysis

The results were presented as mean values with standard deviations unless otherwise specified (continuous parameters) and with percentages and frequencies (categorical variables). Statistical significance was considered as a p-value of less than 0.05. Comparative group analysis was performed using χ^2 Pearson test with Yates' continuity correction for dichotomous parameters and Student's t-test for continuous variables. A logistic regression model with multiple-chance odds ratios was performed. All analyses were performed using the software package Statistica (version 12.5, StatSoft Inc., Tulsa, OK, USA).

Results

The analysis of quantity and the division of the studied population

The study group was composed of 102 patients with newly diagnosed ischemic stroke. All of them underwent neuroimaging examination i.e. Computed Tomography (CT) or magnetic resonance (MR). As a result of scans, Leukoaraiosis (LA) was diagnosed in 24.5% of hospitalized patients (GSC). Other patients, without typical changes for LA, constituted a control group (GC), which was compared with a group of patients with LA (Fig. 1).

Comparative analysis of demographics and pharmacotherapy in the study group

Both GSL and GC were composed of more women than men. The sex does not have an impact on the occurrence of leukoaraiosis. The patients with LA were older than CG ($p < 0.001$).

In both groups, a high level of comorbidities classified as risk factors for stroke was found. The most common comorbidities were hypertension, dyslipidemia and obesity. There was no difference in the frequency of these diseases in both GSL and GC.

Smokers constituted lower rate in group of patients with LA ($p = 0.015$). Compared to non-smokers, significantly lower age was observed, at which patients with addiction suffered from a stroke (66.4 ± 9.8 *vs.* 75.1 ± 11.6; $p = 0.005$).

There was a significantly lower heart rate in the LA group, although remaining within the reference values (68 ± 10 *vs.* 77 ± 13; $p = 0.003$). However, there were no differences in the blood pressure values between both groups.

The analysis of the ongoing pharmacotherapy showed that differences in the administration of beta1-adrenolytics are present in patient with *vs.* without LA ($p = 0.03$). Their use is associated with a 3 times less frequent occurrence of LA. No correlation was observed with other groups of medicines.

Details about the characteristics of both groups were presented in Tables I and II.

Comparative analysis of laboratory tests in both groups

It is worth mentioning a dissimilarity in blood parameters that was observed. In the GSL group, the hemoglobin value was lower than in GC ($p = 0,03$), as well as a higher amount of platelets ($p = 0.04$). No other differences in blood test were noticed.

Differences in lipid parameters were observed. LA patients presented a higher than the upper limit of the normal value of LDL cholesterol level ($p = 0.04$) and a slightly higher value of total cholesterol ($p = 0.08$), moving towards the significance of statistical value.

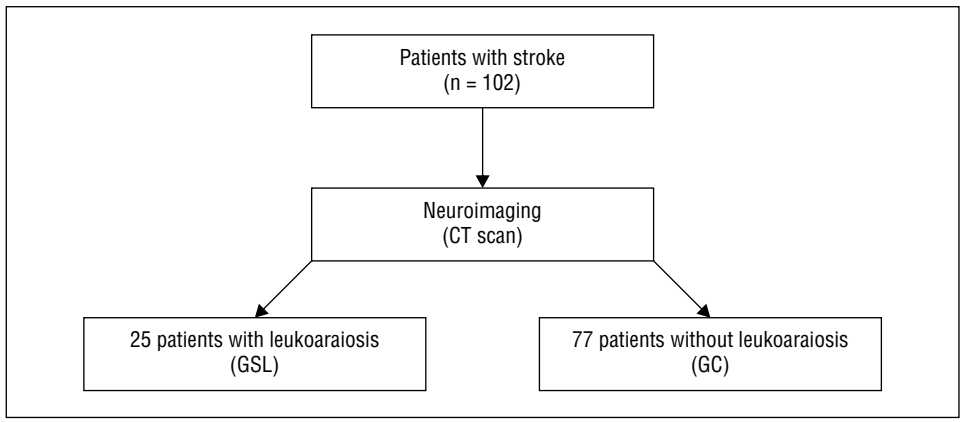

Figure 1. Study flow chart. GC — control group; GSL — study group with leukoaraiosis; CT — computed tomography

Table I. Clinical characteristic of the study groups

Variable	GSL (n = 25)	CG (n = 77)
Age* (years)	77.9 ± 7.1	68.6 ± 11.8
Males	8 (32%)	38 (49.4%)
BMI > 30 [kg/m^2]	7 (29.4%)	32 (41.3%)
Stroke in the past	6 (24%)	17 (22.1%)
Myocardial infarction in the past	3 (12%)	16 (20.8%)
Brain trauma in the past	1 (4%)	4 (5.2%)
Hypertension	22 (88%)	71 (92.2%)
IHD	8 (32%)	22 (28.6%)
Dyslipidemia	18 (72%)	45 (58.4%)
Depression	4 (16%)	8 (10.3%)
Diabetes Mellitus	7 (28%)	24 (31.1%)
Smoking*	4 (16.7%)	44 (56.7%)
HR*[bpm]	68 ± 10	77 ± 13
Systolic BP [mm Hg]	144 ± 24	136 ± 28
Diastolic BP [mm Hg]	77 ± 12	79 ± 18
Alcohol drinking	1 (4%)	13 (16.9%)

Data presented as means ± standard deviation (SD) or number (percent) of subjects; BMI — body mass index; BPM — beats per minute; GSL — study group with leukoaraiosis; CG — control group; IHD — ischemic heart disease; HR — heart Rate; BP — blood pressure; *p < 0.05 study group (GSL) *vs.* control group

Table II. Comparison of the ongoing drug regimens between the studied groups

Drug class	GSL (n = 25)	GC (n = 77)	p-value
Statins	24 (96)	68 (88)	0.27
DHP-CCB	7 (28)	30 (39)	0.33
Beta-blockers	7 (28)	41 (53.2)	0.03
Nitrates	3 (12)	5 (6.5)	0.38
Diuretics	11 (44)	31 (40.2)	0.74
ACEIs/ARBs	18 (72)	47 (61)	0.33
PPIs	10 (40)	35 (45.5)	0.64
NSAIDs	0 (0.0)	3 (3.9)	0.32
ASA	16 (64)	50 (64.9)	0.93
NOAC or VKA	4 (16)	18 (23.3)	0.44

DHP-CCB — dihydropyridine calcium channel blockers; ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; PPIs — proton pump inhibitors; NOAC — non-vitamin K antagonist oral anticoagulant; NSAIDs — non-steroidal anti-inflammatory drugs other than ASA; ASA — acetylsalicylic acid; VKA = vitamin K antagonists; GC — Control group; GSL — Study group with leukoaraiosis

Detailed results of laboratory tests of both groups are presented in Table III.

Comparative analysis of imaging research, neurological condition and cognitive functions in both groups

In GSC, higher average values of CIMT in carotid arteries were noted. The thickness of IMC in left common carotid artery was 1.1 ± 0.3 in GSL group and 0.95 ± 0.2 in GC group (p = 0.02) (Fig. 2).

The relation between leukoaraiosis presence and NIHSS scale score was not demonstrated (p = 0.50).

The results of neurological examinations of patients from both groups were compared, however, no significant differences were found in the results.

The relationship between the presence of leukoaraiosis and cognitive disorders was noted. Patients with GSC scored lower in a Clock-Drawing test than patients from the control group. Median score of Clock-Drawing test in a group of patients with LA was 1, meanwhile, other patients obtained 5 points (p = 0.04). However, no link between the occurrence of leukoaraiosis and the results of MMSE test was evident.

The detailed results are presented in Table IV.

Table III. Laboratory results of the study groups

Variable	GSL (n = 25)	GC (n = 77)
MMSE adjusted for age and education [points]	22±7	24±6
HCT (%)	38.5±5.8	39.8±5.9
RBC [×10^{12}/L]	4.4±0.4	4.4±0.5
HGB [g/dL]*	12.9±2.4	13.8±1.5
WBC [×10^9/L]	8.1±1.9	8.9±4
PLT [×10^9/L]*	279±101.2	238.3±72.4
HDL level [mmol/L]	1.3±0.3	1.2±0.4
LDL level* [mmol/L]	3.5±1.2	2.6±1.1
Total cholesterol [mmol/L]	5.2±1.3	4.6±1.4
Triglycerides [mmol/L]	1.6±0.9	1.6±0.9
Serum albumin [g/L]	40.5±3	40±4.4
Serum protein [g/L]	68.6±5.8	66.8±5.6
CRP [mg/L]	8±9.5	14.7±31
Creatinine [μmol/L]	99.7±64.9	89.7±36

Values presented as means ± standard deviation (SD) or percentage of subjects; MMSE — Mini Mental State Examination Scale; HCT — hematocrit; RBC — red blood cell; HGB — hemoglobin; WBC — white blood cell; PLT — blood platelets; HDL — high-density lipoprotein; LDL — low-density lipoprotein; CRP — C-reactive protein; GC — Control group; GSL — Study group with leukoaraiosis; *p < 0.05 study group (GSL) *vs.* control group (GC)

Prediction of leukoaraiosis based on the interview and basic laboratory test results

The logistic regression analysis of selected variables was performed. Univariate analysis showed that several clinical variables are related to the presence of LA i.e.: age, LDL-levels and the use of beta-adrenoreceptor antagonists. However, no relationship was evident–dihydropyridine calcium channel blockers. The presence of leukoaraiosis can be predicted with a sensitivity of 83% and specificity of 70%.

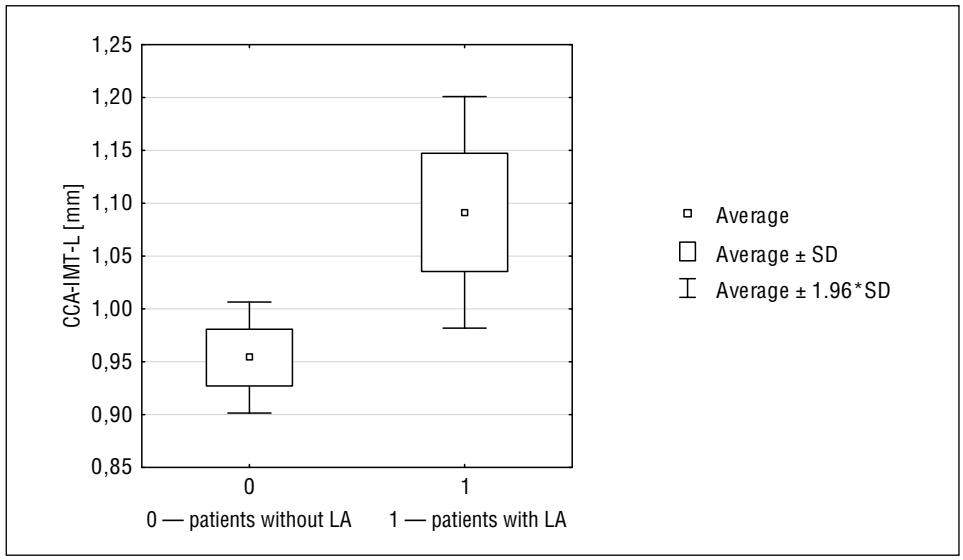

Figure 2. Comparison of the value of intima-media thickness (IMT) common left carotid artery (CCA-L) in both groups; p = 0.02

Table IV. Neurological findings upon physical examination in study groups

Variable	GSL (n = 25)	GC (n = 77)
Muscle strength on Lovett's scale	3.5 ± 0.9	3.8 ± 1.1
Abnormal tendon reflexes	3 (12)	16 (20.8)
Sensory disturbance	1 (4)	5 (6.4)
Ataxia*	8 (32)	13 (16.9)
Presence of neurological abnormalities upon PE	5 (20)	31 (40.2)
NIHSS score upon admission	5.6 ± 3.7	6.5 ± 4.2
CN-III, CN-IV, CN-VI palsies*	2 (8)	1 (1.3)
CN-V palsy	1 (4)	1 (1.3)
CN-VII palsy	4 (16)	7 (9.1)
CN-VIII palsy	4 (16)	7 (9.1)
CN-X palsy	4 (16)	14 (18)
CN-XII palsy	5 (20)	23 (30)

Values presented as means ± standard deviation (SD) or number (percent) of subjects. NIHSS — National Institutes of Health Stroke Scale; CN — cranial nerve; PE — physical examination; GC — control group; GSL — study group with leukoaraiosis; *p < 0.05 study group (GSL) *vs.* control group (GC)

Table V. Associations of selected variables with the presence of leukoaraiosis. Univariate logistic regression analysis

Variable	OR (95% CI)	p-value
Age	1.01 (1.04–1.16)	0.002
DHP-CCB use	0.61 (0.27–1.63)	0.32
Beta-blockers use	0.34 (0.13–0.91)	0.03
Serum-LDL concentrations	1.83 (1.21–2.78)	0.005

DHP-CCB — dihydropyridine calcium channel blockers; LDL — low density lipoprotein; OR — odds ratio; CI — confidence interval

Discussion

Leukoaraiosis is a significant clinical problem. It very often occurs among people with a newly recognized stroke, moreover, it also occurs in the general population. [7, 9, 14] Our study confirms the wide dissemination of lesions typical for LA in the population of patients after a stroke, what was noted in almost every fourth patient (Fig. 1). Although the etiology of LA has not been clearly established, it is known that its occurrence intensifies under the influence of typical cardiovascular risk factors [6, 7]. It can, therefore, be assumed that with the improvement of human living standards and changes in dietary structure, we will observe an increase in the incidence of LA in the population [14].

Previous research revealed that the incidence of LA increases with age. The age range not only affects the frequency but also the severity of symptoms that are associated with LA. Our study confirmed these reports because we showed that the occurrence of LA gradually increases with age, with a similar pattern in men and women. It is hard to unequivocally determine the age limit above which the risk of LA increases rapidly, as it seems that this risk increases gradually over the next decades of life. Most publications indicate age over 60 as a risk factor for LA [7, 14]. Our results remain more optimistic, showing that a significant increase in risk occurs in the eighth decade of life.

Previous studies have shown that the incidence of LA is significantly higher in women than in men, suggesting that female sex is a significant risk factor for this disorder. Although in our study we did not show a statistically significant influence of gender,

it is worth noting that women dominate in GSL (Tab. I). Considering a similar profile of diseases and disorders associated with both sexes, it seems that a higher incidence of LA in women is associated with physiological differences (including brain morphology, hormone levels) [7, 15]. There is also a hypothesis that it was the loss of the protective effect of estrogen after menopause that is of significant meaning [16].

The results of our study clearly indicate that the presence of leukoaraiosis correlates with the severity of other cardiovascular risk factors [6, 7]. One of them is the occurrence of higher LDL values in the serum of patients with LA, exceeding the acceptable norms (Tab. III). This is an interesting observation because, despite the well-known atherogenic effect of LDL, it does not equal with the risk of LA development. Only a few studies have linked high levels of LDL with leukoaraiosis, showing not so much of an increase in its occurrence, as intensifying the symptoms and intensity of changes in patients with LA already present [7, 17]. In our studies, we presented a positive correlation between abnormally high LDL values and the occurrence of LA. The majority of previous reports linking lipid disorders with leukoaraiosis showed a significant effect of elevated triglycerides and the presence of metabolic syndrome on the frequency of changes in periventricular white matter brain structures [7, 14]. However, we have not confirmed this relationship.

Our analysis also showed that patients with LA differ from the control group regarding the values of traditional blood count parameters. In GSL, significantly lower hemoglobin values than those in GC were found, although they did not meet the criteria adopted by WHO (Tab. III). It cannot be unequivocally determined what effect these lower values of hemoglobin had on LA development. However, it is worth mentioning, that anaemia in older patients has proven to affect cognitive functions impairment, executive dysfunctions in particular, as well as reduced physical fitness and increased mortality [18]. Thus, it affects the severity of symptoms that may be the symptoms of leukoaraiosis [11]. After taking these relationships into account, it must be assumed that the value of hemoglobin may have an influence on the pathogenesis of LA, even if the decrease is small (in the lower limits of the proper value). Undoubtedly, this issue requires a thorough analysis and more research, however, it cannot be ruled out that it may play a role in explaining a higher percentage of women in GSL. We also observed in the study that LA was associated with a significantly higher number of platelets (Tab. III). This observation is difficult to explain, but it requires attention due to the fact that the earlier studies have shown a relationship between the platelet volume (MPV) and the risk of LA lesions [19]. Therefore, the influence of a higher number of thrombocytes on the pathogenesis of changes in the white matter is also likely.

The presence of leukoaraiosis correlates not only with deviations in laboratory tests' results but also abnormalities in imaging examinations. One of them is significantly higher rate of CIMT in left common carotid artery (CCA) in patients with LA (Fig. 2). This observation is in line with previous research reports, which also associated improperly high IMT values with the risk of LA [20]. This information supports a more complex etiology of changes in the white matter than assumed so far. Currently, the theory is that their pathogenesis is based mainly on microvascular ischemia [11]. High IMC values indicate that the macrovascular component also plays a role, and LA is associated with chronic cerebral hemoperfusion. It is not without significance that only left-side changes in the IMT value are observed. It is probably related to the difference in hemodynamic stress resulting from the anatomical differences of carotid arteries' places of the inlet. These stresses may be exacerbated by hypertension, which in our study concerned 88% of patients in GSL. It is also worth noting that LA had a higher severity on the left side, which indicates the interrelationship of these irregularities [20, 21].

An important aspect of our study was the demonstration of the protective effect of beta-blockers. As already mentioned, their use was associated with a threefold decrease in the incidence of LA (Tab. II). Previous reports have shown that the use of antihypertensive drugs is associated with a smaller intensity of changes in the white matter of the brain, but they did not show any advantage of any group of drugs [22]. It is worth noting that, considering the slower heart rate found in GSL, beta-blockers protective function is unlikely to result from their basic negative chronotropic activity (Tab. I). The observed phenomenon may result from the pleiotropic mechanism, often attributed to this group of medications.

Numerous publications indicate that LA is manifested by cognitive dysfunctions, slower thinking, emotional dullness and limitation of spontaneity [23, 24]. However, its unambiguous influence on cognitive functions of patients is difficult to demonstrate. In our study, we used the clock drawing test and MMSE to assess patients in this field. The results we have obtained also remain ambiguous. We were able to demonstrate the impact of LA on a significant reduction in the results of the clock drawing test, but we did not obtain significant differences in MMSE

results (Tab. III). The group led by Genlong Zhong received slightly different results, that still left space for doubts. They showed that the incidence of LA correlates with worse results of MMSE, while the intensity of these changes does not affect the results [25]. Based on current knowledge, it can be assumed that LA affects cognitive functions, but the precise determination of its role requires further research.

Leukoaraiosis can also be subclinical, producing less severe symptoms, incorrectly identified as natural changes associated with ageing. It should be underscored that in this case it is a significant risk of stroke, as well as a cardiovascular disease and they are associated with higher mortality [1, 7, 13]. Therefore, early identification of patients with LA is important, in which the prediction model presented in our work may be helpful, based on information on age, LDL values and pharmacotherapy.

Limitations of the study

The study was single-center, non-randomized and carried out on a small group of patients, so our results may not be generalized. To confirm our conclusions, a large randomized clinical trial is needed. In order to confirm the usefulness of a multiple-sensitivity of LA prediction model, it would be necessary to carry out a study assessing the occurrence of LA in patients who fulfil the criteria for the risk of the presence of LA, before they experienced a stroke.

Conclusions

The presence of leukoaraiosis in patients with stroke is a common finding, and it is closely related to cognitive impairment. Both, the ongoing pharmacotherapy and the number of coexisting cardiovascular risk factors may alter its course.

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