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Carotid intima-media thickness better differentiates between groups of stroke patients and persons without cerebrovascular disease than other conventional and novel risk factors

Radosław Kaźmierski[1], Cezary Watała[2], Edyta Podsiadły[3], Jolanta Dorszewska[4], Zofia Adamczewska-Goncerzewicz[4], Stanisława Tylewska-Wierzbanowska[3], Wojciech Kozubski[1]

[1]*Department of Neurology, University of Medical Sciences, Poznań, Poland*
[2]*Department of Haemostatic Disorders, Medical University, Łódź, Poland*
[3]*Department of Bacteriology, National Institute of Hygiene, Warszawa, Poland*
[4]*Department of Neurochemistry, University of Medical Sciences, Poznań, Poland*

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When measured by ultrasound, the morphological markers of carotid atherosclerosis such as intima-media thickness (IMT) and cross-sectional plaque area have been associated with the risk of ischaemic stroke. We set out to determine whether the morphological parameters of the carotid arteries made it possible to better differentiate between groups of older atherothrombotic stroke patients and persons without cerebrovascular disease than conventional and novel risk factors of stroke.

Of the total number of 623 persons examined, 54 stroke patients (mean age 63.3 years) and 74 controls without cerebrovascular disease (mean age 66.3 years) fulfilled the inclusion criteria for this investigation and were enrolled in the case-control study. After adjustment for age, gender and education level, the strongest associations were found between stroke and carotid IMT [odds ratio (OR) = 10.6; 95% confidence interval (CI): 4.3–26.9] and plaque area (OR = 5.4; 95%CI: 2.3–13.1). Other risk factors showed weaker associations with stroke occurrence. Of the clinical risk factors, a significant association was found between stroke and coronary heart disease (OR = 3.5; 95%CI: 1.2–10.2), hypertension (OR = 3.2; 95%CI: 1.5–7.2) and smoking (OR = 2.7; 95%CI: 1.1––6.4). From the laboratory-derived risk factors a significant association was found between stroke and triglyceride levels (OR = 4.4; 95%CI: 1.9–10.0), and an inverse correlation was observed between stroke occurrence and HDL-cholesterol level (OR = 0.4; 95%CI: 0.2–0.8).

The carotid IMT and plaque area, measured with the use of ultrasonography, showed a better correlation with stroke occurrence than currently recognised clinical and biochemical risk factors. The intima-media thickness and plaque area of the carotid arteries could be useful parameters in the development of strategies to identify patients at high risk of atherothrombotic ischaemic stroke.

Key words: atherosclerosis, brain infarction, carotid plaques, ultrasonography

Address for correspondence: Radosław Kaźmierski, MD, Laboratory for Cerebrovascular Research, Department of Neurology, University of Medical Sciences, ul. Przybyszewskiego 49, 60–355 Poznań, Poland, tel: +48 61 869 14 54, fax: +48 61 869 16 97, e-mail: R.Kazmierski@am.poznan.pl

INTRODUCTION

In clinical practice the physician often wishes to identify those patients at risk of ischaemic stroke and to decide which of them require more aggressive medical therapy. This can be difficult, especially in older patients, most of whom present with a variety of risk factors of atherosclerosis. The influence of each single risk factor on the development of carotid and cerebral atherosclerosis and the risk of stroke may have changed during the patient's lifetime. Some of these risk factors (such as hypertension) may have been diagnosed previously and treated for some time, while others may have been dependent on environmental circumstances, such as previous infections with *Chlamydia pneumoniae (C. pneumoniae)*. Features of the patient's life-style such as smoking, over-eating, stress and levels of physical activity may also have changed with time. Since the physician examines the patient at a given moment in the patient's life, it is impossible to assess all the risk factors which may have had an influence on that patient in the course of that life. In spite of ongoing progress in the identification of novel risk factors such as high plasma homocysteine and lipoprotein (a) [Lp(a)] concentration, *C. pneumoniae* infection or increasing serum C-reactive protein (CRP) concentration [26], it is possible that some risk factors are not recognised at all. Spence et al. [29] estimated that only half the plaques measured with the use of ultrasound can be explained by the usual risk factors.

Under such circumstances there is an urgent need for a simple and inexpensive test which is independent of more or less precise knowledge of the patient's previous and current risk factors that can help in assessing the risk of stroke. A possible tool for the assessment of stroke risk is high sensitivity B-mode ultrasonography of the carotid arteries [6, 9, 21, 33]. Previous prospective studies which focused on the relation between carotid intima-media thickness (IMT) and ischaemic stroke were adjusted for a relatively small number of conventional risk factors and did not take into consideration the novel risk factors [6, 21, 33]. Knowledge of the correlation between stroke occurrence and various conventional and novel risk factors could be helpful in the development of strategies to identify high-risk patients and to improve physicians' decision-making processes regarding the adjustment of therapeutic and preventive methods.

We set out to determine whether morphological carotid artery wall parameters measured by ultrasound, such as IMT or cross-sectional plaque area, allow better differentiation between older atherothrombotic stroke patients and age and gender matched persons without cerebrovascular disease than is afforded by other conventional and novel atherosclerosis risk factors.

MATERIAL AND METHODS

Sample

Of the total of 623 persons who attended the Laboratory for Cerebrovascular Research of our Department of Neurology during the period from January 2001 to June 2002, 54 patients with atherothrombotic stroke (including 29 males) fulfilled the inclusion criteria of the study. The stroke patients were referred by their physicians for the assessment of atherosclerosis of their carotid and vertebral arteries. The mean interval between stroke and participation in the study was 4.2 ± 2.2 years.

The control group consisted of 74 persons (including 36 males) without cerebrovascular disease who attended a local club for senior citizens drawn from a variety of backgrounds. The controls were recruited from members of the club in the same proportion with regard to educational background as the stroke patients. The level of education of the patients and controls was self-reported during the demographic interview and classified for the purpose of this study by years of education, i.e. Group 1: ≥ 15 years, Group 2: 11–14 years, Group 3: ≤ 10 years.

There were 17 (31.5%) stroke patients as compared to 23 (31.1%) controls in the first educational group and 26 (48.1%) stroke patients to 36 (48.6%) controls and 11 (20.4%) stroke patients to 15 (20.3%) controls in the second and third groups respectively. The differences in education between the groups were not statistically significant. The mean age of all the subjects was 65.0 ± 7.9 years, 63.3 ± 7.2 for the stroke patients, and 66.3 ± 8.5 for the controls.

Exclusion criteria

The exclusion criteria took account of the fact that it has recently been demonstrated that one-year treatment with statins is sufficient to induce IMT regression [31] and also that *C. pneumoniae*-positive patients treated with macrolid antibiotics show reduced progression of carotid atherosclerosis [27]. In the present study, therefore, we excluded patients treated with these drugs.

Recent infectious disease, brain infarction and myocardial infarction (MI) are related to increased leukocyte counts, plasma fibrinogen levels and CRP

serum levels [4, 28, 36]. Subjects who had experienced any infectious disease within 6 months and a stroke or MI within 12 months prior to the commencement of the study were not included. Those who had undergone carotid surgery or angioplasty were also excluded from the study. The study only concerned patients with atherothrombotic stroke and so did not include patients for whom full hospital records, including those for head-computed tomography (CT) or magnetic resonance imaging (MRI), were not available. We did not include patients with cardiac sources of cerebral embolism such as atrial fibrillation, mitral stenosis or a mechanical prosthetic valve or those in whom ultrasound examination revealed a hipokinetic left ventricular segment or a left ventricular thrombus. Patients with a lacunar stroke diagnosed by CT or MRI were also excluded as were patients with a suspected stroke of other or undetermined etiology.

Inclusion criteria

The TOAST ischaemic stroke classification system was used in the study [2]. Only the stroke patients who fulfilled the TOAST criteria for thrombo-embolic stroke ("large-artery stroke") were included in the study.

Ultrasonography

Carotid IMTs were assessed using high-resolution ultrasound (Sonoline Sienna, Siemens with 7.5 MHz probe). All the subjects were examined in the supine position by the same sonographer (R.K.). The left and right arteries were scanned by a longitudinal ultrasound image of the far walls of the arteries in both the antero-posterior and lateral planes.

The carotid IMTs were assessed, by the same sonographer (R.K.), as previously described [17]. In brief, for the purpose of the evaluation, the carotid artery was divided into 3 segments based on arterial anatomy. The first segment included the distal 2-cm of the vascular wall of the common carotid artery (CCA) immediately proximal to the dilatation of the bifurcation. The second segment, the carotid bulbs (BULB), was defined as the segment between the carotid dilatation and the flow divider of the internal and external carotid arteries. The third segment, the internal carotid artery (ICA), was defined as the segment immediately distal to the tip of the flow divider over a 1 cm distance. The loss of the parallel wall configuration, which marks the origin of the bulb segments, was easily identified as a consistent marker of the distal end of the CCA segment (Fig. 1).

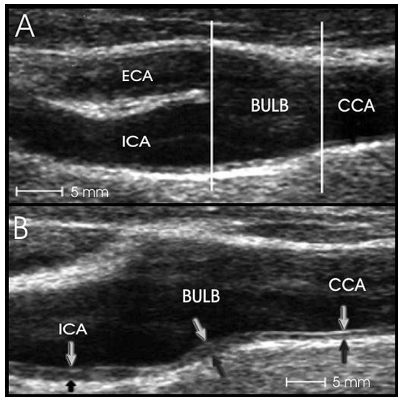

Figure 1. A. High-resolution ultrasound longitudinal image of the distal common carotid artery (CCA), the bulb (bifurcation), the proximal internal (ICA) and external (ECA) carotid arteries as defined by the study protocol; **B.** The arrows indicate intima-media thickness on the far wall of the carotid artery segments.

Plaque was defined as a local thickening of the intima and media protruding into the lumen, with a thickness exceeding 100% of the mean IMT of the segment in a given plane.

The cross-sectional area of the plaque was assessed, by the same sonographer (R.K.), as described by Spence et al. [30]. In brief, the plane in which the measurement of each plaque was made was chosen by panning around the artery until the view showing the largest extent of that plaque was obtained. To shorten the time of ultrasound examination of each patient the images were frozen and stored on 3.5 inch diskettes for off-line analysis. Afterwards, each plaque cross-sectional area was measured off-line by tracing around the perimeter with a cursor on the scanner screen. The cross-sectional area of the plaque was assessed with the use of the scanner's software [30]. If there were two or more plaques in the same artery the sum of all the cross-sectional areas of all the plaques seen in the carotid artery was taken as the total plaque area. Additionally, the Duplex colour mode was used to ensure that no hypoechogenic (echolucent) plaques were missed in the region examined.

The reproducibility of the measurement of IMT, evaluated according to the Bland-Altman method, has been described elsewhere [17].

The reproducibility of the measurement of the carotid plaque cross-sectional area was also evaluated according to the Bland-Altman method [5]. The mean intraobserver difference between double measurements performed on a sample of 20 patients was 0.18 mm^2 (95%CI: –7.94–8.30).

Clinical evaluation

A standardised questionnaire to provide information about demographic background, occupation, education and medical history was completed at each examination. Blood pressure measurements were taken twice, at the beginning and end of the study session, after 10 minutes rest in the sitting position. Subjects were considered hypertensive if they had, on both measurements, systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mm Hg, or if they were taking antihypertensive medications. Subjects were defined as diabetic if the fasting glucose level was ≥ 7.00 mmol/L (126 mg/dl) or if they were taking antidiabetic medications. They were classified as smokers if they smoked at least 1 cigarette per day; as non-smokers if they had never smoked or as ex-smokers if they had given up smoking > 1 year previously (for the purpose of this study we pooled the current and ex-smokers). Stroke, coronary heart disease (CHD) and myocardial infarction was diagnosed on the basis of the history and the patient's hospital and out-patient records.

The body mass index (BMI) was calculated for each subject. Blood was drawn once, after 12 hours of fasting. Serum lipoproteins were measured using standard enzymatic methods (Synchron CX 7 analyser, Beckman, USA) and LDL cholesterol (LDL-C) was calculated by the Friedewald formula [13]. Serum glucose was assessed with the use of an EBIOBASIC glucose analyser (Eppendorf, Germany). The leukocyte count was measured by an automated method (Sysmex K4500, USA) and the fibrinogen plasma concentration was assessed by nephelometry (Nephelometer ACL 100, IL, USA). The plasma concentrations of homocysteine, methionine and cysteine were measured with the use of high-performance liquid chromatography (Gynkotek, Germany) with an electrochemical detector (CoulArray 5600, ESA, USA), as described elsewhere [1].

CRP and Lp(a) serum concentrations were measured with a high-sensitive immunoassay and determinations were performed with the Behring Nephelometer BN II (Dade Behring, Germany), according to the method described elsewhere [19, 23]. Levels of *C. pneumoniae*-specific IgG and IgA serum antibodies were determined by enzyme immunoassay with a major outer membrane protein complex as diagnostic antigen (ELEGANCE *C. pneumoniae* IgG & IgA ELISAs, Bioclone, Australia). Concentrations of chlamydial antibodies were expressed as the index (optical density of the sample/cut-off value). The tests were carried out according to the manufacturer's instructions.

Written informed consent for blood sampling and ultrasound examination for research purposes was obtained from each person included in the study and the study protocol was approved by the Medical School Ethics Committee.

Statistical analysis

Data are given as mean ± SD, and for non-normal measurements (the Shapiro-Wilks W test) as the geometric mean and 1 SD range ($\bar{x}_G$; ± 1SD). For data showing no departures from normality (according to the Shapiro-Wilks test) we used the standard unpaired Student t test. The Mann-Whitney U test was employed for the remaining variables to assess the significance of differences between groups. Discrete variables were compared with the use of the test for proportions.

For odds ratio analysis the Mantel-Haenszel Chi-square test we used the opposed values of dichotomised continuous variables from below median range (< Me, rank 0) and above median range (≥ Me, rank 1) or from the 1st (rank 0) and 4th (rank 1) quartiles. The values of the clinical parameters were ranked on the basis of the presence or absence of a given character.

The statistical analyses were made with Statistica version 5.5 (StatSoft, Inc. 2000) and StatsDirect (StatsDirect Ltd. 2000) software.

RESULTS

The morphological parameters for the carotid arteries, as well as the baseline clinical characteristics and biochemical results for the two groups under investigation, are presented in Table 1.

No patients with *de novo* recognised diabetes or hypertension were found in this study and all the patients with these conditions had been treated prior to entry to the study. To avoid statistical bias we did not include diabetes in the analysis, as only one patient from the control group and 11 stroke patients suffered from diabetes.

The ultrasonographically-measured morphological parameters of the carotid arteries such as IMT and mean plaque area demonstrated the most significant differences between subjects with and without stroke.

Plaque occurrence was significantly different between two groups investigated (Table 1). Of the 128 persons, 71 had measurable carotid plaque. There were 44 out of 71 patients (62%) with plaques in the carotid bulbs, and 27 out of 71 patients (38%) with plaques in the internal carotid arteries. In the common carotid arteries the plaques were visible in

Table 1. Baseline carotid IMT, clinical and biochemical characteristics in stroke patients and controls

Variables	Stroke patients (n = 54)	Controls (n = 74)	p
IMT total [mm]	1.11 ± 0.39	0.74 ± 0.26	< 0.0001
IMT CCA [mm]	0.87 ± 0.29	0.64 ± 0.17	< 0.0001
IMT bulb [mm]	1.36 ± 0.52	0.88 ± 0.46	< 0.0001
IMT ICA [mm]	0.93 ± 1.11	0.54 ± 0.71	< 0.0001
Plaque occurrence	42 (78%)	29 (39%)	< 0.0001
Plaque area [mm^2]	36 (16–74)	14 (6–25)	< 0.0001
Total cholesterol [mg/dL]	231 ± 40	230 ± 47	0.958
HDL cholesterol* [mg/dL]	45 ± 12	50 ± 13	0.028
LDL cholesterol [mg/dL]	155 ± 34	152 ± 30	0.967
Triglycerides [mg/dL]	134 ± 48	119 ± 82	0.0005
Lipoprotein (a) [mg/L]	0.10 ± 0.15	0.11 ± 0.21	0.788
Cysteine* [μmol/L]	274 ± 93	282 ± 87	0.311
Homocysteine [μmol/L]	18.3 ± 7.9	15.8 ± 11.1	0.022
Methionine [μmol/L]	21.1 ± 6.7	22.5 ± 10.8	0.188
C. pneumoniae IgG, antibody index	1.44 ± 1.40	1.19 ± 1.01	0.220
C. pneumoniae IgA, antibody index	0.93 ± 0.77	1.02 ± 0.95	0.430
Fibrinogen* [g/L]	4.22 ± 0.86	4.02 ± 0.90	0.237
C-reactive protein [mg/L]	2.86 ± 5.18	1.87 ± 6.51	0.029
Leukocyte count [$\times 10^9$/L]	7.19 ± 2.34	5.58 ± 1.83	0.001
Body mass index* [kg/m^2]	26.2 ± 3.6	25.7 ± 3.1	0.179
Smoking	34 (63%)	25 (34%)	< 0.0001
Hypertension	32 (59%)	23 (31%)	0.001
Coronary heart disease	19 (35%)	8 (11%)	0.0008

*Variables not showing departures from normal distribution are presented as arithmetic means (±SD) and tested with the Student t unpaired test. The remaining continuous variables are shown as geometric means (±SD) and were tested with the Mann-Whitney U test. Plaque area data presented as median and quartile ranges. Discrete variables compared with the use of z test for proportions. All data were standardised for age and data showing differences between sexes were also standardised for sex. Data for plasma fibrinogen and leukocyte count were additionally standardised to smoking.

10 patients, all of whom also had plaques in the carotid bulb.

The odds ratios for the carotid artery morphological parameters and the clinical or biochemical risk factors for stroke, according to the median of the parameters assessed, are shown in Figure 2.

Total IMT and plaque area dichotomised according to quartiles showed more significant correlation than those dichotomised according to the median (OR = 46.0; 95%CI: 8.0–442.4, p < 0.0001 and OR = 12.9; 95%CI: 4.0–43.0, p < 0.0001, respectively).

Hypertension, CHD, smoking and triglycerides were the most significant conventional risk factors derived from both clinical evaluation and laboratory examinations. An inverse correlation between stroke occurrence and HDL cholesterol (HDL-C) was also found to be significant.

No significant correlation was found between stroke and the other parameters, including BMI, total cholesterol (total-C), LDL-C, fibrinogen, Lp(a) and *C. pneumoniae* IgG or IgA antibody indices. Homocysteine and CRP plasma levels were significantly different in the two groups (Table 1), while a significant association with stroke was reached for homocysteine only when dichotomised according to quartiles (OR = 4.8; 95%CI: 1.4–16.7, p = 0.0086), although this association was not significant according to the median (Fig. 2).

DISCUSSION

The results of the present study have demonstrated that the morphological parameters of the carotid arteries measured by ultrasound, such as total IMT and cross-sectional plaque area, show much better

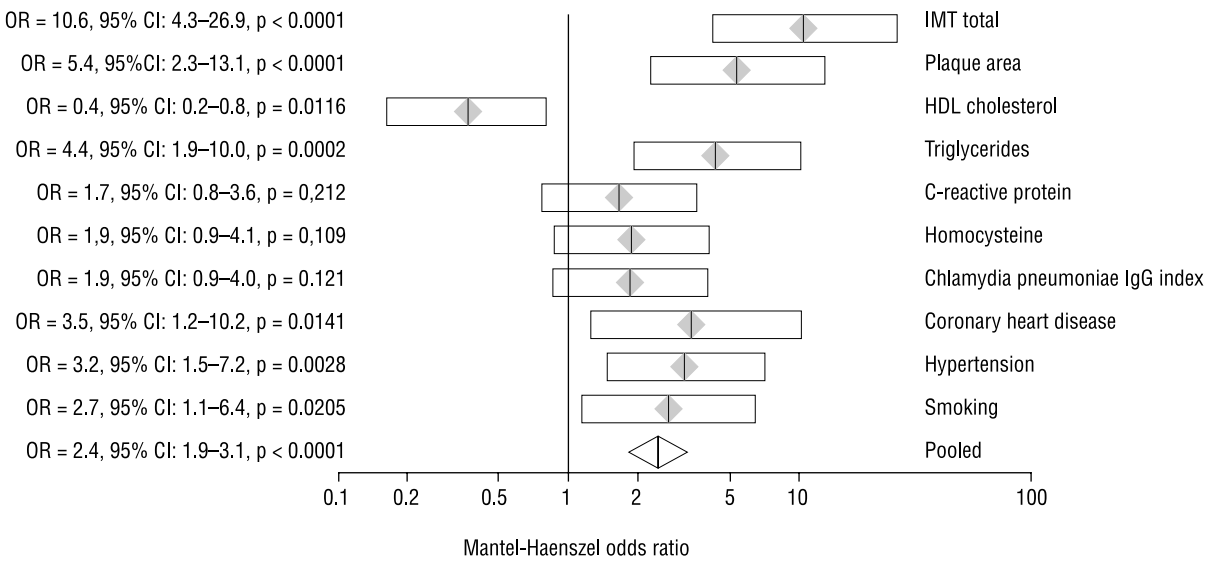

Figure 2. Cochrane odds ratio plot for carotid IMT, carotid plaques and biochemical parameters as risk factors for stroke dichotomised according to median. Fixed effect Mantel-Haenszel Chi-square test of odds ratios was calculated based on conditional maximum likelihood (OR = 2.427; 95%CI: 1.928–3.057). Opposed values of dichotomised continuous variables are from below median range (< Me, rank 0) and above median range (≥ Me, rank 1). OR values presented on a logarithmic scale; 95%CI of OR are displayed as boxes (for a given parameter) or a white diamond (for all pooled parameters) with a central vertical line denoting the odds ratio itself.

associations with stroke occurrence than the other risk factors assessed in the study. We also found that IMT, measured separately in the bulb, common carotid artery (CCA) or internal carotid artery (ICA), also differs significantly in the two groups assessed. The overall cross-sectional area of plaques was also found to be a sensitive marker of stroke risk. Such a result could be expected, since atherosclerosis of the carotid arteries is one of the most important causes of ischaemic stroke among older persons [3, 6]. The strong correlation between carotid IMT, plaque area and the risk of stroke in older adults has been reported in large prospective studies [6, 20, 21, 30, 33]. Furthermore, carotid IMT is regarded as a reliable marker of generalised atherosclerosis [14].

With regard to variables concerning the biochemical risk factors such as triglyceride or homocysteine levels, the association with stroke risk was in line with previous reports [10, 15, 18, 32]. Other plasma thiol compounds, such as cysteine and methionine, have not been shown to be associated with stroke or carotid atherosclerosis [10]. Interestingly, in the present study no correlation was found between total-C and LDL-C and risk of stroke. Large reviews of cohort studies previously undertaken have shown no correlation between any type of stroke and total cholesterol levels in persons aged over 45 [22]. On the other hand, an association was found between the total-C serum level and non-haemorrhagic stroke in men aged 35 to 57 years [15]. It is believed however, that lipids are generally a weaker stroke risk factor among older persons [35]. There is evidence that total-C and LDL-C decreases with age in both men and women [11]. The decline of HDL-C is far more modest, and the total-C/HDL-C ratio increases with age, especially in men [16]. It does not seem surprising that no association between a history of stroke and serum LDL-C and total-C was found in the population examined here, which had a mean age of 65 years, while a negative correlation between HDL-C and stroke occurrence was found. The basal state of HDL-C has been demonstrated to possess anti-inflammatory properties [34], HDL-C mediates the efflux of cholesterol from lipid-loaded cells [24] and a low HDL-C level has been positively associated with carotid atherosclerosis and stroke risk [32].

Since it has been demonstrated that atherosclerosis is a low-grade inflammatory process, inflammatory markers such as CRP may provide a useful adjunctive method for the global assessment of atherosclerosis risk factors [7, 25]. Some pathomechanism mediated by CRP may additionally augment atherogenesis or thrombus formation in the cerebral arteries [7, 8, 12].

In the present study CRP levels differed significantly between stroke patients and controls when compared with the Mann-Whitney U test, although

no significant differences between the groups were evidenced in the frequencies of the higher CRP values according to the estimates of the Mantel-Haenszel odds ratio.

Limitations of the study

The obvious limitation of this study was the relatively small number of subjects and its cross-sectional design. This design was deliberately "broad" (a large battery of tests and a larger number of variables) rather than "deep" (a relatively small population). This was because the aim was to detect trends and associations within a wide range of risk factors that could have a relationship with stroke risk.

The cross-sectional design of the study was as close as possible to the real situation of the consultant in the out-patients department who has to make a therapeutic decision based on the facts which he or she has ascertained at the time of consultation.

CONCLUSIONS

The morphological markers of carotid artery atherosclerosis such as IMT in different segments of the artery and carotid plaque area, when measured with the use of ultrasonography, were demonstrated as significantly larger in the atherothrombotic stroke patients than in the controls without cerebrovascular disease. Clinically-derived risk factors and those assessed in laboratory examination showed, to a lesser extent, the differences between stroke patients and those without cerebrovascular disease, and hence seem less significant in this multi-parametric analysis.

Overall, B-mode high-sensitive carotid ultrasonography appears to be a useful diagnostic tool for differentiating between stroke patients and controls with a mean age of 65 years. The carotid IMT and plaque area measured by ultrasonography meets some of the requirements for an ideal method for the identification of subjects with a high likelihood of developing stroke, since the method is relatively inexpensive, non-invasive, reproducible and readily applicable to an asymptomatic population [20]. Carotid IMT and plaque area could also be helpful in assessing the efficacy of preventive therapy, especially at present, when only approximately half the existing atherosclerotic risk factors can be identified.

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