Early-Onset Carotid Atherosclerosis Is Associated With Increased Intima-Media Thickness and Elevated Serum Levels of Inflammatory Markers

Mária T. Magyar, MD; Zita Szikszai, MS; József Balla, MD, PhD, DHAS; Attila Valikovics, MD, PhD; János Kappelmayer, MD, PhD; Sándor Imre, MD, PhD; György Balla, MD, PhD, DHAS; Viktória Jeney, PhD; László Csiba, MD, PhD, DSci; Dániel Bereczki, MD, PhD, DHAS

Background and Purpose—Several factors have been held responsible for the development of atherosclerosis. To avoid the masking effect of age, we evaluated correlates of carotid atherosclerosis in patients <55 years of age.

Methods—Plasma lipids, oxidative resistance of low-density lipoprotein, homocysteine, inflammatory markers, plasma viscosity, and red cell deformability were measured in fasting blood samples of 100 subjects: 45 patients with >30% stenosis of the internal carotid artery, 20 patients with carotid occlusion, and 35 control subjects. Stenosis and intima-media thickness (IMT) of the carotid artery were evaluated by duplex ultrasound.

Results—White blood cell (WBC) count, plasma fibrinogen, C-reactive protein (CRP), and lipoprotein(a) levels were significantly higher in patients than in control subjects, and patients had increased IMT (P<0.01 for all comparisons).

There was a tendency for higher homocysteine levels in patients. Smokers had higher WBC, fibrinogen, and CRP levels. After the effect of smoking was controlled for, WBC count, natural logarithmic transform of homocysteine, and online-measured IMT remained significantly higher in patients than in control subjects. WBC, fibrinogen, and CRP levels were highest in the highest IMT quartile (P=0.012, P=0.007, and P=0.036, respectively).

Conclusions—Inflammatory markers and homocysteine have a more important role than lipid factors in early-onset carotid atherosclerosis. We cannot recommend the measurement of low-density lipoprotein peroxidation as a routine screening test to identify high-risk patients for early-onset carotid atherosclerosis. The confounding effect of smoking on inflammatory markers should be considered in studies on atherosclerosis. (Stroke 2003;34:58-63.)

Key Words: atherosclerosis ■ homocyst(e)ine ■ inflammation ■ intima-media thickness ■ lipid peroxidation

The consequences of atherosclerosis such as ischemic heart and cerebrovascular diseases rank among the most important public health issues. Increased intima-media thickness (IMT) was reported to occur in an earlier phase of the atherosclerotic process. It has been suggested that common carotid artery (CCA) IMT is a measure of atherosclerosis in general, eg, that CCA IMT correlates with coronary disease, and prospective studies have shown that increased IMT is a powerful predictor of coronary and cerebrovascular complications.

Most publications on carotid artery disease focus on elderly subjects. In a population study of >16,000 people, 90% of subjects affected with severe carotid lesions were >55 years of age. Age is the primary risk factor for carotid artery disease, and examining an elderly patient group may mask the effects of risk factors of early atherosclerosis. Therefore, in the present study, we tried to identify the role of several potential risk factors of early atherosclerosis in a case-control study in subjects <55 years of age.

We were looking for factors that might differentiate young patients with carotid atherosclerosis from those without early atherosclerotic changes in several aspects. Four major alterations were anticipated: (1) we hypothesized that the decreased resistance of low-density lipoprotein (LDL) to oxidative modification is an independent risk factor for cerebral atherosclerosis; (2) we expected that markers of inflammation are increased in patients with early-onset carotid atherosclerosis; (3) we tested plasma viscosity and red cell deformability, as hemorheologic parameters possessed a role in atherosclerosis, and plasma viscosity and found that some red cell parameters correlated with the degree of carotid atherosclerosis; and (4) we expected increased IMT in young patients with occlusive carotid artery disease because IMT was reported to be significantly greater in patients with than in those without carotid stenosis. In addition, we checked previously described alterations because high plasma homocysteine concentrations were reported to be associated...
with an increased risk of extracranial carotid artery sclerosis in the elderly, and lipid levels were also found to correlate with IMT.

**Patients and Methods**

**Patients**

Patients were recruited at the Neurosonological Laboratory of the Department of Neurology, University of Debrecen (Hungary). The upper age limit was set at 55 years. Those with at least a 30% internal carotid artery (ICA) stenosis or occlusion at screening were invited to participate in the study. Of the 20 patients with ICA occlusion, 2 also had contralateral carotid occlusion, 3 had mild scolicotic changes, and 15 had 20% to 80% stenosis on the contralateral ICA. An age- and sex-matched control group was recruited who had no plaques or stenosis of the carotid arteries by duplex examination. Most of these control subjects were treated primarily for tension-type headache, anxiety disorder, or low back pain. After receiving information about the purpose of the study, participants signed a consent form before blood sampling and ultrasound examination. The study was approved by the Ethical Committee of the University of Debrecen.

**Blood Sampling**

Patients and control subjects were asked to come to the laboratory after an overnight fast before taking their morning medications between 7:30 and 8 AM. After they completed a risk factor questionnaire, blood samples were taken. All assays were performed on the day of sampling, and blood samples were kept at room temperature; samples for homocysteine evaluation were kept on ice, and analysis started no later than 90 minutes after blood sampling.

**Analysis of Blood Samples**

Hematologic investigations were performed with the Sysmex SF-3000 (TOA Medical Electronics Co, Ltd) automated hematology analyzer. Fibrinogen was measured by the Clauss method with an ST-A compact coagulometer (Stago). Homocysteine was determined by the Abbott AxSYM system (Abbott Laboratories) with fluorescence polarization immunoassay. Serum lipids and C-reactive protein (CRP) were measured with the Cobas Integra Analyser (Roche) by use of standard laboratory techniques. We used a microassay based on the kinetics of heme-catalyzed lipid peroxidation of LDL to assess the resistance of lipoprotein to oxidative modification. Plasma viscosity was measured with a microviscosimeter (Haake) at 37°C. Erythrocyte deformability was determined by filtering erythrocyte suspension through a Nucleopore polycarbonate filter with a 5-μm pore size (Whatman Inc) using a St George–type filtermeter (Carat Diagnostics). Filtration results were expressed as relative cell transit time.

**Carotid Duplex Ultrasound Investigations**

Ultrasound examinations were performed immediately after blood sampling with a color-coded HP SONOS 2000 (Hewlett Packard) carotid duplex equipment with a 7.5-MHz linear transducer. The investigation included longitudinal and transverse examinations of the carotid arteries. Both diameter and area reductions were measured and calculated at the site of maximal stenosis in the extracranial ICA according to the European Carotid Surgery Trial (ECST) method. Furthermore, the peak systolic and mean and end-diastolic flow velocities in the CCA and in the jet of the ICA stenosis were recorded (angle adjusted). For screening, the ICA stenosis was classified in categories of 10%, taking into account the peak systolic velocity in the jet of the stenosis, broadening of the stenotic and poststenotic spectra, peak systolic velocity in the poststenotic ICA, and direction of ophthalmic flow. A peak systolic velocity of at least 120 cm/s was the threshold for a 50% stenosis. Occlusion was diagnosed in the complete absence of detectable flow in and above the stenosis and the presence of corresponding indirect hemodynamic criteria.

Online measurements of IMT were performed at about 10 mm proximal to the carotid bulb or 20 mm proximal to the flow divider.

IMT was measured between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (upper layer of the adventitia) in the far (deeper) artery wall. All measurements were performed on frozen, enlarged images (2×) at the end of a heart cycle (end diastole), and the transducer was in the mediolateral direction. Measurements were performed in both CCAs, and the larger of the 2 values was used in data analysis. Offline analysis of CCA IMT was made on video images based on the Atherosclerosis Risk in Communities (ARIC) study protocol. IMT was measured in the far walls of the right and left CCAs on the 1-cm segment proximal to the dilatation of the carotid bulb. In each of these 1-cm segments, 11 measurements of IMT were performed at 1-mm increment. The mean IMT of the 22 values in each patient was calculated.

**Statistical Analysis**

Normality of continuous variables was checked by the Sapiro-Wilk test. In case of normal distribution, analysis of variance (ANOVA) and post hoc tests were used. In case of nonnormal distribution, the Mann-Whitney U test and the Kruskal-Wallis ANOVA were used. Frequencies were compared by the Pearson χ² test. Two-way ANOVA was used to control for smoking in group comparisons. Quartiles of the study population were formed by homocysteine, CRP, and IMT values. The role of smoking on IMT was checked in an analysis of covariance (ANCOVA) model in which IMT was the dependent variable, smoking status was the categorical predictor, and serum parameters found to differ between control subjects and patients were used as continuous predictors. Statistical significance was assumed at P<0.05. Statistica for Windows, version 6.0 (StatSoft), was used for data analysis.

**Results**

Demographic characteristics and some traditional risk factors are summarized in Table 1. The mean age in the total group was 48 years with no difference between control subjects and the stenotic and occlusion groups. Men and women were distributed equally in the control and stenotic groups, but most patients with occlusion of the carotid artery were men. There were no differences in the presence of diabetes, heart disease, and family history of cerebrovascular disease among the patient groups and control subjects. Hypertension was more prevalent in the stenotic subgroup than in the others. More patients were smokers. Ischemic stroke and transient ischemic attack were more prevalent in patients than in
control subjects. Men had significantly higher body mass index (29.5±5 and 26.4±4 kg/m², P=0.012) and homocysteine levels (13.2±6.1 and 10.2±4.9 μmol/L, P=0.003) than women. There was no sex difference in inflammatory markers or lipid parameters. No difference was found in inflammatory or lipid parameters, homocysteine, and IMT between patients with and without a history of symptomatic cerebrovascular disease (P>0.05 in all comparisons).

Although parameters were mostly within the normal range, there were several differences in blood parameters among control subjects and the 2 patient groups as indicated in Table 2. White blood cell (WBC) count (P<0.001), fibrinogen (P=0.0009), and CRP (P=0.0012) were higher in patients with occlusive carotid artery disease. Because of the skewed distribution of serum homocysteine, a normally distributed natural logarithmic transform of homocysteine was also analyzed by ANOVA: patients with carotid occlusion had higher values than control subjects and patients with carotid stenosis (P=0.028). Whereas lipoprotein(a) [Lp(a)] was higher in both patient groups than in control subjects, there were no differences among the 3 groups in triglyceride, cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-cholesterol (LDL-C), and apolipoprotein A1 and B levels. There was a significant difference among the 3 groups in IMT from online readings and for mean IMT (the Figure), and the patient groups had thicker intima-media layer in both comparisons (P<0.0001 and P=0.0007, respectively).

Because several parameters seemed similar in the stenotic and the occlusion subgroups, a separate analysis was performed to compare a pooled stenotic and occlusion group with the control group. Whereas levels of inflammatory markers (WBC, P<0.0001; CRP, P=0.0003; fibrinogen, P=0.0002) and Lp(a) (P=0.0042) were significantly higher in patients than in control subjects, homocysteine did not differ from that of control subjects (P=0.2). Both online-measured and mean IMT values were significantly higher in patients than in control subjects (P<0.001).

Smokers had significantly higher WBC count (8.7±2.1 versus 6.9±1.8 G/L), plasma fibrinogen (4.2±1.0 versus 3.4±0.8 g/L), CRP (8.1±11.4 versus 4.5±3.1 mg/L), Lp(a) (410±486 versus 297±469 mg/L), and online-read IMT (1.30±0.33 versus 1.05±0.26 mm) than nonsmokers. Because these factors were higher in patients than in control subjects and more patients than control subjects were smokers (P<0.001), to control for the effect of smoking, a 2-way ANOVA with fixed effects was used with group and smoking status as independent factors. The difference between the 3 groups remained statistically significant for WBC, natural logarithmic transform of homocysteine, and online-measured IMT (P=0.01, P=0.03, and P=0.016, respectively) after controlling for smoking status. Smoking also had an effect on

### Table 2. Blood/Serum Parameters of Study Participants

<table>
<thead>
<tr>
<th>Feature</th>
<th>Controls</th>
<th>Stenosis</th>
<th>Occlusion</th>
<th>P (Kruskal-Wallis ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (G/L)</td>
<td>6.7±1.4</td>
<td>8.5±2.3</td>
<td>8.9±1.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>RBC (T/L)</td>
<td>4.7±0.4</td>
<td>4.7±0.4</td>
<td>4.9±0.4</td>
<td>0.23</td>
</tr>
<tr>
<td>HTC</td>
<td>0.43±0.04</td>
<td>0.44±0.03</td>
<td>0.45±0.03</td>
<td>0.097</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4±0.8</td>
<td>4.1±0.9</td>
<td>4.1±1.2</td>
<td>0.0009</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.7±2.1</td>
<td>7.3±6.4</td>
<td>10.1±17.1</td>
<td>0.0012</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>10.4±2.9</td>
<td>11.7±5.7</td>
<td>15.3±8.4</td>
<td>0.078</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.8±0.9</td>
<td>1.8±1.1</td>
<td>1.9±1.4</td>
<td>0.93</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.7±1.0</td>
<td>5.9±0.9</td>
<td>6.0±1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.3±0.3</td>
<td>1.5±0.5</td>
<td>1.4±0.5</td>
<td>0.071</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.6±0.9</td>
<td>3.6±0.9</td>
<td>3.8±1.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Apo-A1, g/L</td>
<td>1.4±0.2</td>
<td>1.6±0.3</td>
<td>1.5±0.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Apo-B, g/L</td>
<td>1.1±0.2</td>
<td>1.2±0.6</td>
<td>1.2±0.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>240±345</td>
<td>401±436</td>
<td>478±693</td>
<td>0.017</td>
</tr>
<tr>
<td>Δt at Vmax, min</td>
<td>54±9</td>
<td>56±13</td>
<td>54±11</td>
<td>0.972</td>
</tr>
<tr>
<td>Plasma viscosity, mPa</td>
<td>1.36±0.09</td>
<td>1.37±0.09</td>
<td>1.37±0.07</td>
<td>0.87</td>
</tr>
<tr>
<td>Red cell relative transit time</td>
<td>8.1±1.4</td>
<td>8.4±1.3</td>
<td>7.8±1.1</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Values are mean±SD. WBC indicates white blood cells; RBC, red blood cells; HTC, hematocrit; Apo, apolipoprotein.

IMT significantly differs between control subjects and patients with >30% stenosis or occlusion of the ICA (P=0.0007, Kruskal-Wallis ANOVA). For each patient, the mean value of 22 readings (11 on each side) was used.
CRP was no longer different among the 3 groups. The effect of smoking on IMT was further checked in an ANCOVA model in which smoking status was used as a categorical predictor and age, WBC count, Lp(a), CRP, and homocysteine were used as continuous predictors. Of these, smoking ($P=0.006$) were found to be significant predictors of IMT in the whole study population.

To further check whether subgroups differ on the basis of the distribution of some features, quartiles were formed of all subjects (including patients and control subjects) by IMT, WBC count, fibrinogen, and homocysteine. WBC count, fibrinogen, and CRP were the lowest values in the lowest IMT quartile for all parameters (Table 3).

CRP quartiles significantly differed in WBC, fibrinogen, serum total cholesterol, HDL-C, Lp(a), LDL resistance to oxidative stress ($\Delta t$ at $V_{max}$), and online-read IMT, with lowest values in the lowest CRP quartile for all parameters (Table 4).

### Discussion

**Patient Selection**

Examining an elderly patient group may mask the effects of risk factors of early atherosclerosis; therefore, we examined the role of several potential risk factors of early atherosclerosis in young subjects (mean age, 48 years). The prevalence of carotid artery stenosis is low in this age group: 0% and 0.7% of women and 0% and 1.2% of men <50 and <60 years of age, respectively, were reported to have >35% stenosis in the population-based Tromsø Study. In our study, the cutoff for age was 55 years, so the prevalence of carotid stenosis in that age group can be assumed to be <1%. Indeed, we identified the 65 patients <55 years of age with carotid stenosis >30% or occlusion among the >12,000 subjects examined between September 1999 and November 2001. Although our sample was balanced for sex in the stenosis group, most young patients were male in the occlusion group. Male dominance also was characteristic for carotid occlusion in the Tromsø study: all 13 patients with right-sided carotid occlusion of the sample of 6,420 subjects were male.

### TABLE 3. Comparison of Variables in Online-Measured IMT Quartiles

<table>
<thead>
<tr>
<th>Feature</th>
<th>IMT Quartile</th>
<th>$P$ (Kruskal-Wallis ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>WBC (G/L)</td>
<td>7.1±1.7</td>
<td>7.9±2.4</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4±0.7</td>
<td>4.0±1.0</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.3±3.3</td>
<td>8.4±7.5</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.9±1.1</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.8±1.0</td>
<td>5.7±0.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.3±0.4</td>
<td>1.34±0.37</td>
</tr>
<tr>
<td>Homocysteine, $\mu$mol/L</td>
<td>13.1±6.0</td>
<td>10.8±4.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

### TABLE 4. Comparison of Variables in CRP Quartiles

<table>
<thead>
<tr>
<th>Feature</th>
<th>CRP Quartile</th>
<th>$P$ (Kruskal-Wallis ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>WBC (G/L)</td>
<td>6.7±1.8</td>
<td>7.4±1.7</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4±0.7</td>
<td>3.8±1.0</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.6±0.9</td>
<td>1.9±1.1</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.4±0.9</td>
<td>5.9±1.0</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.3±0.3</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>162±229</td>
<td>330±558</td>
</tr>
<tr>
<td>Homocysteine, $\mu$mol/L</td>
<td>10.2±2.8</td>
<td>11.2±3.9</td>
</tr>
<tr>
<td>$\Delta t$ at $V_{max}$, min</td>
<td>48±8</td>
<td>56±10</td>
</tr>
<tr>
<td>Online IMT, mm</td>
<td>1.08±0.33</td>
<td>1.24±0.39</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Potential Role of Lipoprotein Metabolism in Carotid Atherosclerosis

The role of triglyceride and cholesterol in carotid bifurcation atherosclerosis remained controversial even after large angiographic studies.\(^{20,21}\) IMT was found to correlate with LDL-C and triglyceride and to correlate inversely with HDL-C.\(^{13}\) In the fasting state, LDL-C, but not HDL-C and plasma triglycerides, was related to IMT in 50-year-old white men.\(^{22}\) Lp(a) was also suggested as a risk factor for carotid atherosclerosis.\(^{23}\) In the present study, Lp(a) was the only lipid parameter that differed between patients with occlusive carotid artery disease and control subjects.

Homocysteine and Atherosclerosis

The role of homocysteine in atherosclerosis was suggested >30 years ago,\(^{24}\) and high-normal homocysteine concentrations were associated with an increased prevalence of carotid artery wall thickening in a younger patient group.\(^{25}\) Homocysteine exerts its effects through a mechanism involving oxidative damage, including oxidative modification of LDL.\(^{26}\) Moderate hyperhomocysteinemia predicted the severity of cerebral atherosclerosis in patients with cerebral infarction,\(^ {27}\) and a strong association was found between plasma homocysteine and ischemic stroke as a result of large-artery atherosclerosis.\(^ {28}\) Homocysteine was also higher in our patients with occlusive carotid artery disease, but the difference was on the margin of statistical significance.

Plasma Viscosity, Red Blood Cell Deformability, and Atherosclerosis

Plasma viscosity was positively related to mean and maximal carotid artery IMT in the carotid bifurcation in men and women; therefore, Levenson et al\(^ {10}\) suggested that rheological factors are involved in the subclinical phase of atherosclerosis. Rheological factors were very similar across the groups in our study; therefore, we conclude that these factors probably do not have a major role in the early formation of carotid atherosclerosis. The difference in fibrinogen among patients and control subjects in our study was due only to the effect of smoking.

LDL Oxidative Modification and Carotid Atherosclerosis

The oxidation of LDL in the subendothelial space is an early event in atherogenesis.\(^ {29}\) Another hypothesis emphasizes the role of inflammation.\(^ {30}\) Inflammation and lipid peroxidation might have some connection in the development of early atherosclerosis because both IMT and Δt at \(V_{\text{max}}\) were the smallest in the lowest CRP quartile (Table 4). Our finding does not exclude the role of oxidized LDL in the pathogenesis of carotid atherosclerosis. Oxidative modification of LDL takes place in the artery wall under a complex set of conditions affected by plasma components and cell metabolism. Increased oxidative sensitivity of LDL is not the only determinant in oxidative modification of lipoproteins.

Inflammatory Changes and Atherosclerosis

Atherosclerosis is an inflammatory disease; the role of infection in the disease is very controversial.\(^ {7,30}\) Of the inflammatory indicators, elevated CRP was associated with an increased IMT of the CCA.\(^ {31}\) The most consistent finding in our study was the increased level of inflammatory markers (WBC, CRP, fibrinogen) in the patient groups. Fibrinogen was found to be a significant predictor of IMT by several studies.\(^ {32}\) Our finding that smoking explains the difference in fibrinogen among the groups draws attention to the fact that in such studies controlling for smoking should always be performed in data analysis. Some of the differences, however, remained significant among groups after controlling for smoking status, suggesting that smoking by itself cannot explain the increased levels of inflammatory markers in patients with occlusive carotid artery disease.

From our results, we can conclude that oxidative resistance of LDL does not play a marked role in early-onset carotid atherosclerosis, or if LDL oxidation does occur as a local early process in the carotid artery wall, it cannot be assessed by examination of isolated LDL for oxidative resistance. Therefore, measurement of the oxidative resistance of LDL cannot be recommended as a routine screening tool to identify subjects prone to early atherosclerosis. Although homocysteine had a marginally significant role, the higher levels of inflammatory markers suggest that in younger age inflammation might have a more important role in the development of early atherosclerosis than other factors, including serum lipids and homocysteine. Of the modifiable risk factors, smoking has been proved again to be a significant factor in early-onset carotid atherosclerosis, a factor that should be controlled for in studies of atherosclerosis.

Acknowledgments

This study was supported by grants from the University of Debrecen (Mec 16/99), from the Health Science Council of the Ministry of Health of the Hungarian Republic (ETT 490/2000, ETT 578/2000), and from the Hungarian Research Foundation (OTKA No: 037883). We thank Alice Dobolyi and Virág Jánosné for technical assistance.

References


Early-Onset Carotid Atherosclerosis Is Associated With Increased Intima-Media Thickness and Elevated Serum Levels of Inflammatory Markers
Mária T. Magyar, Zita Szikszai, József Balla, Attila Valikovics, János Kappelmayer, Sándor Imre, György Balla, Viktória Jeney, László Csiba and Dániel Bereczki

*Stroke*. 2003;34:58-63; originally published online December 12, 2002; doi: 10.1161/01.STR.0000048845.83285.AC

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/1/58

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/