Italian Multicenter Study on Reversible Cerebral Ischemic Attacks: III — Influence of Age and Risk Factors on Cerebrovascular Atheroclerosis

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SUMMARY The influence of age and other risk factors (history of hypertension and diabetes, cigarette smoking, dyslipidemia) on cerebral atherosclerosis was studied in 462 patients with RIA who had cerebral angiography. The degree of atherosclerosis was quantified using extracranial and intracranial cerebrovascular scores (ECS, ICS) based on the number and severity of the lesion in 11 extracranial and 21 intracranial arterial segments. Thirty-six percent of the patients under age 45 had a normal angiogram compared with 17% of the patients over 45. In the subgroup of patients with abnormal angiogram the mean ECS and ICS vascular scores were not significantly different in the two age groups. Cigarette smoking was the only risk factor to show a strong association with the extracranial score, and it was independent of the effect of age and other risk factors.

STROKES are not only a problem for the old but also for the young population, as the age-specific incidence for cerebrovascular disease (CVD) is more than 20 per 100,000 per year in the population under age 45. Atherosclerosis is believed to be the most frequent cause of cerebrovascular disease in middle age and in the elderly, but a less common cause in the young. The reported decline in mortality and incidence of CVD noted in epidemiological studies has benefited the elderly population more than the young.

Because of this difference, a reliable index of cerebral atherosclerosis in vivo derived from angiographic studies was developed and was correlated with risk factors for CVD present in a large population of symptomatic patients, of different age groups.

Methods

Four hundred and sixty-two patients referred for examination because of carotid or vertebrobasilar ischemic attacks were used in this study. These patients came from six neurological and two neurosurgical centers involved in a multicenter study of stroke in Italy from 1977 to 1981. All patients had clinical symptoms suggestive of single or multiple reversible ischemic attacks (RIAs). Only patients who had cerebral angiography were admitted. Twenty-four patients with a cardiac cause of cerebral ischemic episodes such as atrial fibrillation, recent myocardial infarction and embolic heart disease, were excluded from the study.

Angiography was performed by femoral catheterization with visualization of the presumed symptomatic carotid and/or vertebro-basilar arteries in all patients. Visualization of all extra- and intracranial cerebral arteries was obtained when the presumed symptomatic vascular tree did not show alterations which explained the diagnosis.

All angiograms were evaluated by two neuroradiologists.

The extracranial circulation was subdivided into 11 arterial segments (innominate artery; right and left subclavian, vertebral, common, internal and external carotid arteries). The intracranial circulation was divided into 21 arterial segments, (right and left extradural carotid segments, intradural carotid segments; right and left internal carotid, anterior, median and posterior cerebral, vertebral, posterior inferior, anterior inferior, superior and posterior cerebellar arteries; and basilar artery). A score was used to grade the atherosclerotic process in each abnormal segment, as follows: grade 0.5 — irregularity and tortuosity of the vessel without lumen narrowing; grade 1 — localized plaque with minimal lumen narrowing; grade 1.5 — diffuse or localized 25–50% lumen narrowing; grade 2 — diffuse or localized 50–70% lumen narrowing; grade 2.5 — diffuse or localized 70–90% lumen narrowing; grade 3 — diffuse or localized lumen narrowing of more than
90%. A numerical value for the degree of the atherosclerotic process was obtained by adding the scores of all graded segments. Since the analysis included not only those patients in whom all four vessels were visualized, but those with less extensive angiographic evaluation as well, the scoring was limited to the number of visualized segments for each patient as follows:

\[
\text{score} = \frac{\Sigma \text{ grade of altered segment visualized}}{\Sigma \text{ grade 3 } \times \text{ segment visualized}}
\]

Grade 3 is the score for maximum severity.

Two scores were obtained, one for the extracranial circulation (ECS) with a minimum value of 0.02 and maximum value of 0.82, and one for the intracranial circulation (ICS) with a minimum value of 0.02 and a maximum value of 0.52. The values of 0.82 and 0.52 represent respectively the greatest degree of atherosclerotic involvement for the extra- and intracranial vessels.

Segment scores (ECS, ICS) were used as a measure of the amount of cerebral atherosclerosis. The percentage of patients with abnormal angiogram regardless of the amount, was used to indicate the prevalence of the process in the extra- and intracranial arteries.

The other variables considered in the present analysis were: age, past or present cigarette consumption, history of hypertension, history of overt diabetes mellitus, and alterations of lipid metabolism grouping together dyslipidemias types I, IIa, III, IV, V and IIb. Hypertension and diabetes were anamnestic variables. The result of analysis of these variables determined at the time of entry in the study may differ, and they will be analyzed in greater detail in a subsequent study.

The associations between risk factors, age and abnormal angiogram were determined with an analysis based on the log-linear model of the frequency of each cell. Analysis of variance was used to study the relations between risk factors, age and extra- and intracranial scores.

**Results**

**Characteristics of the Population Studied**

Of the 462 patients 104 (23%) were in the 20–45 year age group and 358 (77%) in the 46–70 year age group. Angiograms were normal in 96 patients (21%). Among the 366 patients with abnormal angiograms (79%), 77 had lesions only of the extracranial vessels, 114 of the intracranial vessels, and in 175 both were involved. Angiography was normal in 36% of the patients between 20 and 45 compared with 17% between 46 and 70 years, this difference is statistically significant (χ² = 14.89, DF 1, p < 0.0001).

In the total population, 177 patients (38%) had hypertension (136 males, 41 females), 66 patients (14%) had diabetes (46 males, 20 females), 246 patients (53%) smoked more than 10 cigarettes/day (230 males, 16 females) and the plasma lipids in 114 patients (25%) were compatible with dyslipidemia (80 males, 34 females). Only the prevalence of hypertension was significantly different in the patients under and over 45 years; it occurred in 44% of the older and in 19% of the younger patients (χ² = 19.6, DF = 1, p < 0.0001).

**Association Between Age, Risk Factors and Abnormal Angiogram**

Results of the analysis according to the log-linear model are shown in table 1. The dichotomous variables analyzed were abnormal angiogram, age, hypertension, diabetes, smoking and dyslipidemia. The analysis was done on all the population separately for those with intracranial and extracranial lesions. The only variable which demonstrated a statistically significant association with altered extracranial angiography was age (χ² = 10.03, p < 0.001). The high probability of finding a normal angiogram in the younger patients was independent of all other variables included in the analysis. None of the risk factors analyzed, either alone in association, correlated significantly with altered extra- or intracranial angiography, since all the second and third level interactions were negative, with exception of age × hypertension.

**Relation Between Age, Risk Factors and Angiographic Scores (ECS, ICS)**

The mean score (ECS) for all the 252 patients with extracranial angiographic alterations was 0.19 ± SD 0.16. The mean score (ICS) in the 289 patients with intracranial alterations was 0.12 ± SD 0.08.

There was a trend for the ECS score to rise with advancing age up to the 40–45 year age group, and then to remain high in the older age groups. The ICS score did not vary with advancing age (fig. 1).

The results of the analysis of variance performed separately for the ECS and ICS scores are shown in table 2. Age alone, or associated with one of the four risk factors, did not correlate significantly with either the ECS or the ICS scores. Of the four major risk factors considered, only smoking was consistently and highly significantly related to the ECS score, (F = 6.07, p < 0.01) and it was independent of age and other risk factors; in fact none of the interactions between smoking, age and other risk factors were significant. Analysis with sex added in the model as an independent variable showed similar results.

**Discussion**

The causes of focal ischemia in young adults are attributable to cerebral atherosclerosis in 50%, to other causes in 30%, and are still unclear in about 20%. In the present study, abnormal angiograms with atherosclerotic alterations were evident in 64% of the young population which in this subgroup may constitute the main or an associated cause of the cerebrovascular episode. Our results showed that in the young patients with abnormal angiograms, the extent of the atherosclerotic involvement of the cerebral vessels was similar to that in older patients. This finding indicates the frequency and importance of cerebral atherosclerosis in the young adult. Others reporting recent and past
Table 1: Association between Age, Risk Factors and Abnormal Angiogram

<table>
<thead>
<tr>
<th></th>
<th>Extracranial lesions</th>
<th>Intracranial lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DF</td>
<td>( \chi^2 )</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>10.03</td>
</tr>
<tr>
<td>History of hyper tension</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
<td>2.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2</td>
<td>3.45</td>
</tr>
<tr>
<td>Age × hypertension</td>
<td>1</td>
<td>0.59</td>
</tr>
<tr>
<td>Age × diabetes</td>
<td>1</td>
<td>1.89</td>
</tr>
<tr>
<td>Age × smoking</td>
<td>1</td>
<td>0.00</td>
</tr>
<tr>
<td>Age × dyslipidemia</td>
<td>1</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Table 2: Relationship between Age, Risk Factors and Angiographic Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Extracranial score</th>
<th>Intracranial score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DF</td>
<td>F</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td>History of hyper tension</td>
<td>1</td>
<td>1.85</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1</td>
<td>0.32</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
<td>6.07</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2</td>
<td>0.67</td>
</tr>
<tr>
<td>Age × hypertension</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>Age × diabetes</td>
<td>1</td>
<td>2.61</td>
</tr>
<tr>
<td>Age × smoking</td>
<td>1</td>
<td>0.13</td>
</tr>
<tr>
<td>Age × dyslipidemia</td>
<td>2</td>
<td>2.59</td>
</tr>
</tbody>
</table>

Series, have reached similar conclusions. These reports demonstrate a high prevalence of risk factors for atherosclerosis in young patients with cerebrovascular disease especially when compared with the prevalence found in a normal population of similar age. These results emphasize the particular importance of smoking and dyslipidemias.

In atherothrombotic stroke, the Framingham Study found a higher frequency of young men who smoked and young adults who had dyslipidemias. In the population we studied, the associations between smoking and cerebral atherosclerosis and between dyslipidemia and cerebral atherosclerosis in the 20-45 year group were not different from those found in the 46-70 year group. When the results are analyzed in more detail, it is seen that the young dyslipidemics have a higher extracranial score (ECS) when compared with the older age group (fig. 2); however, the difference does not reach the significance level with multifactorial variance analysis (table 2). The mean extracranial score of patients who smoked was on the other hand not different in the two age groups (fig. 2), although smoking was the only factor associated with a higher degree of extracranial atherosclerosis (table 2).

An association between cigarette smoking and cerebrovascular disease is accepted by many, but strong evidence for the association is lacking. Since the habit of smoking is widespread, it could be that the...
main effect of this factor is masked by the effect of other associated factors. In our patients, the athero-
genic effect of smoking in patients with cerebrovascu-
lar disease was evidently independent of the other fac-
tors analyzed (table 2). This also correlated with the se-
verity of exposure, as there was a positive relation-
ship ($F = 3.56, DF = 3; 25, p < 0.025$) between the num-
ber of cigarettes smoked and the extracranial athe-
rosclerotic score (fig. 3). Although the mech-
isms by which smoking may enhance risk of stroke
are still unknown, it seems reasonable to deduce from
our results that there may be a causal relationship be-
tween smoking and amount of atherosclerosis.

In conclusion, the results of our angiographic study
showed a higher prevalence of abnormal cerebral an-
giography in older patients with RIAs compared with a
similar clinical group aged less than 45 years. In the
two age groups studied there were the same relation-
ships between the degree of cerebral arteriosclerosis
and risk factors such as hypertension, diabetes and
dyslipidemias. This implies that the influence of risk
factors is similar not only in the elderly but also in the
young population. Of all the factors considered, the
most important is cigarette smoking, equally in the
young as well as in the elderly.

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References
1. Schoenberg BS: Epidemiology of cerebrovascular disease. South
2. Garraway WM, Whisnant JP, Furlan AJ et al: The declining inci-
3. Soltero I, Liu K, Cooper R et al: Trends in mortality from cerebro-
vascular diseases in the United States, 1960 to 1975. Stroke 6:
549–558, 1978
4. Fieschi C, Argentino C, Rasura M: Italian study of reversible isch-
5. Fieschi C, Mariani F, Brambilla C, Prencipe M et al: Italian multi-
center study on reversible ischemic attacks I: population character-
istics and methodology including clinical reliability. Stroke 14:
424–430, 1983
Ltd, London, 1977
1: The analysis of case-control studies, 192–279 IARCL, Lyon,
1980
9. Candelise L, Pinciroli D: Cerebral ischemia in young adults. Ital J
Neurol Sci 1: 257–262, 1980
10. Grnndal AB, Cohen RJ, Saul RF, Taylor JR: Cerebral infarction in
932–938, 1967
12. Hindfelt B, Nilsson O: Brain infarction in young adults with par-
ticular reference to pathogenesis Acta Neurol Scand 55: 145–157,
1977
13. Snyder BD, Ramirez-Lasseras M: Cerebral infarction in young
14. Marshall J: The cause and prognosis of strokes in people under 50
15. Chopra JS, Prabhakar S: Clinical features and risk factors in stroke
16. Mettinger KL, Söderström CE: Pathogenetic profile of TIA before
17. Fogelholm R, Aho K: Ischaemic cerebrovascular disease in young
adults. I. Smoking habits, use of oral contraceptives, relative
18. Fogelholm R, Aho K: Ischaemic cerebrovascular disease in young
adults. 2. Serum cholesterol and triglyceride values. Acta Neurol
19. Kannel WB: Epidemiology of cerebrovascular disease. In: Cere-
bral Arterial Disease. Ed RW Ross Russel. Churchill Livingstone,
20. Nomura A, Comstock GW et al: Cigarette smoking and strokes
Stroke 5: 483–486, 1974
21. Friedman GD, Dales LG, Ury HK: Mortality in middle-aged smok-
22. Editorial: How does smoking harm the heart. Br Med J 281:
573–574, 1980

APPENDIX
Special Project Ischemic Brain Disease OD2
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