ITALIAN MULTICENTER STUDY ON REVERSIBLE CEREBRAL ISCHEMIC ATTACKS: VI — PROGNOSTIC FACTORS AND FOLLOW-UP RESULTS

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SUMMARY A total of 462 patients (mean age 52 years) affected by reversible focal ischemic attacks (RIAs) were followed prospectively in 8 neurologic institutions in Italy for 4 years. All cases were evaluated with a cerebral angiography and 21% of angiograms were normal. At the end of the follow-up period the cumulated probability for death, stroke, cardiac event and new RIA was respectively 7%, 8%, 3% and 36%.

The predictive value of the baseline characteristics of this series was evaluated by a multifactorial analysis which showed that RIA and stroke (specific cerebrovascular risk) were more likely to develop in patients with a history of more than one RIA and in those in whom multiple vascular territories were involved. Moreover, previous myocardial infarction, intermittent claudication, angina pectoris, time elapsed since the first attack, and duration and severity of the attack itself were independently associated with general cardiovascular risk (death, stroke and myocardial infarction). We conclude that predictive factors, and thus also pathogenetic mechanisms, may be different for general cardiovascular risk and specific cerebrovascular risk in RIA patients.

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TRANSPORT CEREBRAL ISCHEMIC ATTACKS (TIAs) are considered predictors of stroke, myocardial infarction and death. Reports on the natural history of patients with TIAs vary, with mortality rates ranging from 1% to 16% per year, and stroke rates from 1% to 8% per year.1-3 The most reliable data are those obtained in community studies.4,5,12 However, consecutive and prospective hospital series may also provide valuable information on long-term outcome and predictive associated factors in patients with TIAs.

This report presents an analysis of the results obtained in one of such series. They were based on a multicenter, prospective study performed in Italy between 1977 and 1983, with recruitment of 462 patients out of a consecutive series of 622 cases with reversible cerebral focal ischemic attacks (RIAs). The subjects were followed for a minimum of 4 years after diagnosis.

MATERIAL AND METHODS

This was a prospective, multicenter study performed in 8 neurological centers in Italy. Recruitment started on January 1, 1977 and ended on June 30, 1979. Follow-up was completed on June 30, 1983. A standardized protocol was used for collecting baseline and follow-up data.24-25 The characteristics of the patients involved, the selection and inclusion criteria have been presented in the previous paper.24

Patients

All consecutive patients referred to the Clinical Units for one or more RIAs in the preceding 12 months and aged less than 70 years were considered eligible. In fact, 70% of them had had a RIA within 1 month, and 4% within 3 months.

The following patients were excluded: those with general or cardiological contraindications to cerebral angiography, an incomplete or unsuccessful angiographic study, neurologic disease other than cerebrovascular, severe disease placing them at risk of death within the following 4 years, and those who refused to participate.

CLINICAL FINDINGS

Sex, age at entry, interval from first and from last RIA to entry, number of attacks and duration of each episode were recorded. In addition, the following characteristics of the attacks were noted: Diagnostic type. RIA patients were subdivided into 3 groups according to the subjective duration of symptoms and the results of detailed neurological examination: a) TIA, symptoms lasting less than 24 hours (in fact 28% lasted for less than 1 hour) and normal neurological examination; b) Prolonged TIA (P-TIA), symptoms lasting more than 24 hours, but with normal neurological examination after 4 weeks or less; c) TIA with incomplete recovery (TIA-IR), symptoms lasting less or more than 24 hours, but with minimal residual signs at neurological examination 4 weeks later.26 Vascular territory. Based on established criteria27 this was defined according to the symptoms recorded as carotid (right or left), vertebrobasilar, or undefined. In patients with more than one attack occurring in both carotids or in carotid and vertebrobasilar territories, the territories were defined as multiple.
Angiographic findings

Cerebral angiography was performed in all patients. Visualization of extra- and intracranial arteries of the symptomatic territories was complete in 100% of the cases, and in 74% at least 2 vascular territories were visualized. The angiograms were read centrally by two neuroradiologists, and were considered abnormal if an atherosclerotic lesion was observed by both radiologists in any segment of the vascular tree. Angiography was completely normal in 96 patients, and 366 showed arteriosclerotic lesions. In the latter group, the degree of arteriosclerosis was quantified using separate extracranial (E.C.S.) and intracranial (I.C.S.) cerebrovascular scores.28

An appropriate lesion was defined as a stenotic lesion of over 25% in a vascular tree ipsilateral to the clinical territory.

Risk factors

The risk factors analyzed were: history of hypertension (history of more than two readings greater than 150/90 mm Hg); values of systolic and diastolic blood pressure during hospitalization; smoking more than 10 cigarettes/day; history of diabetes (history of fasting blood sugar higher than 120 mg% or abnormal glucose tolerance test); fasting blood glucose level during hospitalization; dyslipidemias (grouping together types I, IIa, II, IV and IIb); total cholesterol and triglycerides level; alcohol consumption and body mass index (weight/height$^2$).

Extracerebral arteriosclerosis

This was recorded at entry as: a) previous myocardial infarction; b) intermittent claudication; c) history of angina pectoris, using Rose and Blackburn’s questionnaire.29 Electrocardiographic findings were also evaluated. ECG readings were done locally, following a standardized protocol, and they were considered abnormal whenever significant disorders of heart rate, dysrhythmias, or signs or necrotic lesions were detected.

Follow-up and medical and surgical treatments

In all cases, follow-up visits were performed regularly every 6 months, for a mean of 4 years (mean 4.6 years) or until a major event such as stroke or death occurred; this permitted to repeat the clinical, neuropsychological and laboratory examinations, that will be reported separately, monitor the treatment carefully and control the risk factors.

Patient compliance was in fact very good throughout: 20 cases only (4%) required ‘home monitoring’ and further investigations in order to ascertain the occurrence of end-points, and only one of the 462 was lost to follow-up. All patients underwent the treatment prescribed by the attending physician. As a result, vascular surgery was performed in 17% of the patients; 2% were given protracted treatment with oral anticoagulants; in 39% aspirin was prescribed, and in 42% the only treatment suggested was careful control of risk factors. This was done in all patients in addition to other treatments.

Antiaggregants were continued in 11% of patients even after surgery.

Follow-up events

During the follow-up, deaths, strokes, MIs and new RIAs were recorded. The latter were subdivided into three diagnostic groups: TIA, P-TIA and TIA-IR. Diagnosis of MI was assessed by a cardiologist and based on the presence of at least two of the following: prolonged chest pain, serum enzymatic alterations, QS changes at ECG. Stroke was defined clinically as a sudden onset of focal permanent neurological deficit, confirmed by at least one neurological examination after 4 weeks in surviving cases, and by CT scan in 70% of the cases. Deaths were attributed to stroke, to cardiac cause (including all sudden deaths), or to nonvascular cause (24%). It is important to note that each event was verified by the P.I. who personally examined all clinical records to avoid any intra-observer differences.

Statistical analysis

A total of 29 variables were analyzed for this report. Life tables and univariate analysis, adjusted by center, were elaborated using the log-rank approach, also known as the Mantel-Haenszel chi-square test for survivalship data.30 Events were recorded quarterly. Continuous variables were categorized in three levels using clinically accepted criteria. End-points analyzed only by univariate analysis, were new RIAs, strokes, MIs and deaths.

For evaluating the prognostic value of the variables for a specific cerebrovascular risk and for a general cardiovascular risk, the endpoints were aggregated in two groups: RIAs and/or strokes and deaths or strokes or MIs. Variables selected as significant by the univariate analysis, plus age and sex, were used to perform a backward multivariate analysis by the SAS PHGLM procedure,31 which fits Cox’s linear regression model. Proportionality was checked by plotting the -log(-log S) curves for different strata of variables and the models fitted by plotting the residuals.

Results

The series consisted of 462 patients, 340 males and 122 females, mean age 52.3 (SD = 10.1). One hundred and sixty other patients were excluded according to stated criteria (see Methods). Therefore, we analyzed the results of a cohort representing 75% of a consecutive series of hospitalized RIAs in Italian institutions, excluding patients older than 70 years and those with severe heart diseases.

In a four-year period, 257 patients remained asymptomatic, 144 presented new RIAs (TIA 76%, P-TIA 16%, TIA-IR 8%), 36 presented a subsequent stroke that was hemorrhagic in 5, and 16 had a major cardiac event (table 1). The reversible ischemic attacks were 4 times more frequent than strokes, and the latter were more than twice as frequent as the cardiac events.
There were 34 deaths; fatal strokes accounted for 44% of them, heart diseases for 32%.

The cumulative probability of RIA at 1 year was 23%, at 2 years 30%, at 3 years 35% and at 4 years 36%, therefore there was an initial peak of risk for repeated RIA. One the contrary, the curve for stroke, cardiac event and death rose slowly and regularly throughout the follow-up period (fig. 1).

Univariate Analysis

This analysis was performed in order to evaluate the potential predictive value of variables recorded at entry. The results are summarized in table 2 (†). The end points analyzed only by univariate analysis were: new RIAs, strokes, MIs and deaths. The occurrence of these events was not significantly influenced by age and sex of patients, nor by medical and surgical treatments received.

None of the risk factors appeared to predispose specifically to new cerebrovascular events in this series in which all treatable conditions were accurately monitored and controlled during the entire follow-up period. Only the probabilities of cardiac event and death were significantly higher in patients with raised blood pressure, and in those with high fasting glucose levels.

The extracerebral arteriosclerotic diseases, listed in table 2, showed a potential predictive value. The probability of stroke was higher in patients with abnormal ECG (12.1% versus 6.0%; p = 0.029), in patients with a previous diagnosis of MI (24.6% versus 7.2%, p = 0.002) and in those with a history of intermittent claudication (26.9% versus 6.8%; p = 0.012).

The cumulative probability of cardiac events after 4 years was 7.4 and 2.8% in patients respectively with and without ECG abnormalities (p = 0.025); 18.5 and 3.1% in patients with and without previous MI (p < 0.001); and 10.9 and 3.4% in patients with and without a history of intermittent claudication (p = 0.024).

The cumulative mortality rate was 12.1 and 6.0% in patients respectively with and without ECG abnormalities (p = 0.024); 31.7 and 6.3% in patients with and without a previous MI (p < 0.0001); and 19.9 and 6.8% in patients with and without a history of intermittent claudication (p = 0.026).

Table 2 also shows the potential predictive value of the neurological features and of neuroradiological angiographic data. Four out of 6 clinical characteristics of the attacks, and 1 out of 4 angiographic variables, correlated with the occurrence of a new cerebrovascular event using a univariate analysis.

The cumulative probability of stroke was higher in patients with RIAs in multiple vascular territories (18.7%) than in those with only carotid (7.3%) or vertebrobasilar territories (4.1%; p = 0.025). Also the diagnostic type was predictive for stroke: TIAs strictly defined presented a favorable prognosis: in fact no stroke occurred in the 75 patients with this diagnosis, whereas in P-TIAs and in TIA-IR the cumulative probability of stroke was 12.5 and 9.3% (p = 0.021).

When the interval between first attack and entry was longer than 6 months, the probability of stroke was also higher: 12.4 versus 4.1% recorded in patients with a more recent first episode (p = 0.01). The above characteristic is related to the number of attacks, since 99% of patients with a disease history of over 6 months had more than one episode. However, the number of attacks alone did not seem to be predictive of stroke.

The number of attacks, although not relevant for predicting strokes is an important warning sign of new impending RIAs: the probability of patients with more than 1 attack at entry developing a new RIA was 41.0% whereas in patients with a single attack it was 24.1% (p = 0.003). Finally, new RIA could be anticipated also by the degree of the arteriosclerotic involvement of the extracranial arteries. In fact the probability
of recurrent RIAs was higher (45.5%) in patients with moderate E.C.S. than in patients with low E.C.S. (27.6%) and also in those with severe E.C.S. (33.8%; $p = 0.021$). Thirty-eight percent of the latter had undergone vascular surgery. As expected, none of the above findings except for the time interval elapsed since the last cerebrovascular episode, was predictive of new cardiac events and deaths.

**Multivariate analysis**

As the next step, the independent effect of each variable was analyzed by Cox's regression hazards model (table 3).

In order to evaluate the variables significantly associated with the risk of subsequent stroke and/or RIA (specific cerebrovascular risk) age, sex and the following variables, identified as significant by the univariate analysis, were introduced in the model: a) vascular territory; b) number of attacks; c) angiographic E.C.S.; d) ECG; e) previous MI; f) history of intermittent claudication.

The vascular territory and number of attacks were the only variables that remained in the model at the end of the analysis, and that were therefore independently related to a specific cerebrovascular risk in this cohort. Since the angiographic lesion was associated with age, as previously described, it did not show a predictive value in the multifactorial analysis.

Another group of variables were examined in a multivariate analysis of factors associated with general cardiovascular risk (death, stroke and MI), and the results are shown in table 3. Significantly and independently associated with general cardiovascular risk were previous MI, intermittent claudication, angina, time elapsed since the first attack, duration and severity of the attack itself (P-TIA and TIA-IR versus TIA). Number of attacks, ECG, age and sex were the other variables included in the multifactorial analysis, but they did not show any independent association with the end-points analyzed.

**Discussion**

With an annual mortality of 2% and a stroke rate of 2%, the present cohort of 462 patients with focal reversible ischemic attacks is one of the hospital series with favorable outcome. Comparison between different series presents considerable difficulties due to the

| Table 2: Potential Prognostic Variables for New Ischemic Attack, for Stroke, for Myocardial Infarction and for Deaths Analyzed by Log-rank Approach |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | RIA (162)*      | Stroke (36)     | Cardiac event (17)† | Total deaths (34) |
| age             |                 |                 |                 |                 |
| sex             |                 |                 |                 |                 |
| history of hypertension |                 |                 |                 |                 |
| systolic blood pressure |                 |                 |                 |                 |
| diastolic blood pressure |                 |                 |                 |                 |
| smoking, cigarettes/day |                 |                 |                 |                 |
| history of diabetes |                 |                 |                 |                 |
| blood glucose |                 |                 |                 |                 |
| dyslipidemias  |                 |                 |                 |                 |
| blood cholesterol |                 |                 |                 |                 |
| blood triglycerides |                 |                 |                 |                 |
| alcohol consumption |                 |                 |                 |                 |
| obesity, weight/height |                 |                 |                 |                 |
| ECG abnormalities |                 |                 |                 |                 |
| angina pectoris |                 |                 |                 |                 |
| myocardial infarction  |                 |                 |                 |                 |
| intermittent claudication |                 |                 |                 |                 |
| vascular territories |                 |                 |                 |                 |
| number of attacks |                 |                 |                 |                 |
| duration of attacks |                 |                 |                 |                 |
| months from first RIA |                 |                 |                 |                 |
| months from last RIA |                 |                 |                 |                 |
| diagnostic type |                 |                 |                 |                 |
| abnormal angiogram |                 |                 |                 |                 |
| E.C.S.  |                 |                 |                 |                 |
| I.C.S.  |                 |                 |                 |                 |
| appropriate lesion  |                 |                 |                 |                 |
| surgical treatment |                 |                 |                 |                 |
| medical treatment |                 |                 |                 |                 |

*Including 18 patients with subsequent major events (14 strokes, 4 MI); †including 1 nonvascular death.

$\dagger p \leq .05; \ddagger p \leq .01; \dagger p \leq .001$.

| Table 3: Independent Predictive Variables at 4 Years of Follow-up, Based on Cox's Regression Analysis |
|-----------------|-----------------|-----------------|-----------------|
| End-points      | Variables       | β               | $\chi^2$      | p               |
| RIA and stroke  | vascular territories (multiple vs carotid) | 0.581           | 9.60           | 0.0019          |
|                 | number of attacks (more than one vs one) | 0.591           | 9.75           | 0.0018          |
| Death, MI and stroke | angina pectoris (presence vs absence) | 1.333           | 6.45           | 0.0111          |
|                 | myocardial infarction (presence vs absence) | 1.290           | 12.58          | 0.0004          |
|                 | intermittent claudication (presence vs absence) | 1.193           | 12.42          | 0.0004          |
|                 | months from first RIA (more than 6 vs less than 6) | 0.666           | 6.05           | 0.0139          |
|                 | diagnostic type (P-TIA, TIA-IR vs TIA) | 2.421           | 5.75           | 0.0165          |
variability in baseline clinical characteristics, selection criteria, duration of follow-up and type of treatment. Since mortality and cardiovascular morbidity increase with the mean age of patients in the different series, the low mean age (52.3) may partly explain the low incidence of stroke and death recorded in this series. Moreover, an estimate of stroke rate also depends on the definition of stroke which varies in the different studies. In fact strokes have been defined in other studies as all events with symptoms and/or signs persisting beyond 24 hours, and what we define as P-TIA or TIA-IR (minor persisting neurologic signs) may be classified as strokes elsewhere. The statistical advantages of the latter extensive definition is to increase the number of end-points in therapeutical trials, but it is somewhat arbitrary from a clinical viewpoint. If we combine P-TIA and TIA-IR events with strokes, the annual stroke rate of the present study increases from 2 to 4%, which is comparable with the figures in the Canadian Cooperative Study and the AICLA study.

The value of this study lies not so much in the general outcome in this series, but in the analysis of the factors predicting outcome that may be useful in future studies as well as in clinical practice.

The multifactorial analysis suggests that more than one attack at entry (fig. 2) and attacks in multiple vascular territories (fig. 3) are independent significant predictors of subsequent cerebrovascular events. This result, in accordance with the findings of some previous authors, seems to support the hypothesis that subsequent cerebrovascular events are mainly of embolic origin.

Other studies identified short attacks, the recent ones, and carotid TIAs as those with unfavorable outcome: none of these variables correlated with cerebrovascular outcome in our series.

There is no general agreement on the prognostic value of angiographic features in RIA's. Some reports describe no association between abnormal angiography and the incidence of subsequent cerebral vascular events. Others report a significant association with a higher incidence of stroke, TIA and stroke, cardiac event and stroke, and cardiac event alone. In this series none of the angiographic variables was independently associated with subsequent cerebrovascular events.

Further analysis of the subgroups is in progress to clarify the pathogenetic value of these results although they are probably, at least in part, due to the low resolution power of conventional angiography. The bias of our series that excluded elderly and severe cardiologic patients may explain the predominance of stroke deaths (44%) over cardiac deaths (32%), contrary to previous reports. Yet cardiac disease implied an unfavorable cardiovascular outcome also in this series (fig. 4). Since peripheral vascular disease was also an independent predictor of poor outcome (fig. 5), we believe that the increased risk of death and major vascular events was related to the severity of the underlying diffuse atherosclerotic condition rather than to a specific complication of the associated heart disease alone.

Although this study is based on a selected cohort of RIA patients, it provides some pathologic and prognostic guidelines that might help to clarify the mechanism of subsequent major cardiovascular events and death (general cardiovascular risk) and of stroke or RIA (specific cerebrovascular risk). The former largely depends on the diffuse atherothrombotic condition and presumably on its rate of progression whereas the latter is mostly related to current embolic mechanisms,
especially as far as recurrent RIAs are concerned. This phenomenon is an expression of the active phase of the disease, since the events are clustered in the months immediately following the clinical warning event.

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Appendix
Special project ischemic brain disease OD2 participant units
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Risks of Carotid Endarterectomy

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SUMMARY An objective, retrospective review of 358 carotid endarterectomies performed in the neurosurgical teaching units of the University of Toronto in the year 1982 demonstrated a perioperative stroke rate of 3.9% and a death rate of 1.5%.

Most (82%) surgical neurological complications occurred after the immediate post-operative period (24 hours). This high incidence of delayed stroke suggests that most perioperative strokes are embolic rather than hemodynamic. Careful operative technique and the use of anticoagulants and antiplatelet agents may be more important in preventing postoperative deficits than intraoperative monitoring and intraluminal shunting.

Our figures and those of current published data indicate that a 5–6% combined morbidity and mortality should be expected in carotid endarterectomy. These data are critical both to decision making with the individual patient as well as in the planning of future carotid surgery trials.

EVALUATION OF CAROTID ENDARTERECTOMY for stroke prevention requires realistic expectations about perioperative morbidity and mortality. Published stroke and death rates vary from less than 2%,1,2 to almost 25%.3 Surgeons tend to report lower figures,4–8 while higher rates emerge from citywide3,9 or multi-centre experience,10 usually reported by neurologists.

Although carotid endarterectomy as an effective means of stroke prevention has been practiced for years, its efficacy has never been properly evaluated.11 The need for a prospective study using modern methodology is long overdue. Feasibility and study design require knowledge of expected stroke and death rates for a relatively large group of surgeons.

This study reports results in a large consecutive series of procedures performed in the Toronto teaching hospitals and differs from most previous studies with respect to the objective manner in which data was collected and analysed.

Methods

All surgeons in the five adult neurosurgical teaching units of the University of Toronto agreed to participate in the study. Consecutive cases of carotid endarterectomy in the calendar year 1982 were reviewed. Protocols were devised which identified cases by study, number only, omitting identity of the patient, surgeon and hospital.

A study coordinator (MCZ) experienced in stroke research, transferred relevant information from the hospital charts to data entry forms using pre-determined definitions of carotid stroke and transient ischemic attack (TIA).

Questionable or missing entries were reviewed by the principal investigators (a neurosurgeon and a neurologist) who requested additional information as necessary. The principal investigators remained “blind” and only the study coordinator had direct access to hospital charts. Participating neurosurgeons agreed to protocol design and authorised chart review on their own cases. They did not review data entry forms, nor did they have any input into their completion.

Neurological deficits lasting more than 24 hours were classified as cerebral infarction, providing the corresponding computed tomography (CT) did not show evidence of hemorrhage. The designation of cerebral infarctions as “major” and “minor” retrospectively, on the basis of persisting neurological deficit, is too subjective to be reliable. Focal neurological deficits lasting less than 24 hours were classified as transient ischemic attacks. Perioperative neurological complications were defined as those occurring during hospital admission, with onset up to twelve days postoperatively.

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