Multiple modifiable risk factors for first ischemic stroke: a population-based epidemiological study

D. I. Hadjiev\textsuperscript{a}, P. P. Minev\textsuperscript{b} and M. I. Vukov\textsuperscript{a}

\textsuperscript{a}Medical University, Sofia, Bulgaria; and \textsuperscript{b}Medical Faculty, Thracian University, Stara Zagora, Bulgaria

Keywords: lifestyle-associated risk factors, multiple risk factors, outcomes, prevalence

Received 1 January 2003
Accepted 17 April 2003

The aims of this epidemiological population-based cohort study were to examine the prevalence of the multiple modifiable vascular risk factors, their distribution patterns and outcomes among a Bulgarian urban population. A total of 500 volunteers, 200 men and 300 women, without clinical signs and symptoms of cerebrovascular disease, aged 50–79 years, were enrolled in the study. A structured questionnaire, physical examination, electrocardiogram records, a battery of laboratory tests and carotid duplex scanning were employed. Three or more modifiable vascular risk factors were detected in 52% (260/500) of the subjects. Dyslipidemias, hypertension, obesity, cigarette smoking and cardiac diseases were found to be the most prevalent single risk factors. Asymptomatic carotid stenosis (ACS) of 50% or greater was detected in 8.8% (23/260) of the volunteers examined. After a 2-year follow-up, 2.7% (7/260) of the persons with modifiable vascular risk factors reached the end point transient ischemic attacks (TIAs), ischemic stroke and myocardial infarction. The following combinations of risk factors among the subjects enrolled in the study were significantly associated with these outcomes: hypertension and cardiac diseases (OR = 6.82; 95% CI, 1.21–38.41), cardiac diseases and obesity (OR = 6.13; 95% CI, 1.27–29.72), ACS and high low-density lipoprotein (LDL) cholesterol levels (OR = 11.11; 95% CI, 1.58–78.29). The identification of subjects with multiple vascular risk factors may be important for primary medical or surgical stroke prevention.

Introduction

Several population-based epidemiological studies have focused on identification of risk factors for ischemic stroke (Wolf et al., 1983, 1988; Wannamethee et al., 1995; Stegmayr et al., 1997; Feigin et al., 1998; Manchev et al., 2001). However, the impact of risk factors for stroke is not fully understood nor is the possible benefit of their multimodality therapy (Goldstein et al., 2001). Few studies are dealing with the distribution patterns and outcomes of multiple stroke risk factors (Paffenbarger and Wing, 1971; Whisnant, 1997; Hadjiev et al., 1999; Whisnant et al., 1999).

The well- and less well-documented modifiable vascular risk factors often occur in clusters. Vascular risk factors are also known to interact to multiply the risk of stroke (Kannel, 1976; Lechner et al., 1986).

Different combinations of risk factors for stroke have been described (Paffenbarger and Wing, 1971; Kannel, 1976; Lechner and Samastur, 1997; Hadjiev et al., 1999). The Framingham profile consisting of elevated systolic blood pressure, elevated serum cholesterol level, glucose intolerance, cigarette smoking and left ventricular hypertrophy as determined by electrocardiogram (ECG) identifies persons at highest risk for stroke (Kannel, 1976).

Geographic variation in the distribution and control of multiple vascular risk factors has been observed, which may contribute to differences in stroke incidence and mortality rates between countries (Stegmayr et al., 1997; Lechner and Hadjiev, 1998; Lechner et al., 1999).

The Austrian–Bulgarian population-based cross-sectional epidemiological survey on vascular risk factors has shown different distribution patterns of the risk factors among Austrian and Bulgarian urban populations. The risk factor combinations are more prevalent among Bulgarian townspeople. It has also been suggested that the high incidence and mortality rates for stroke in Bulgaria, could be, at least partly, attributable to the high prevalence of hypertension and to the frequent occurrence of combinations of vascular risk factors (Hadjiev, 1998; Lechner and Hadjiev, 1998).

However, the prevalence of multiple vascular risk factors and their impact on the risk of first ischemic stroke have not been studied frequently.

This population-based biennial epidemiological survey has been designed to assess the prevalence of the multiple vascular risk factors, their distribution patterns and outcomes among the Bulgarian urban population.
Subjects and methods

This prospective epidemiological study was carried out in the University city of Stara Zagora, which has 147,932 inhabitants. The persons enrolled in the survey were examined from 1997 through 2000.

A preliminary study, using the methods described below, was performed to determine the sample size. Three and more than three modifiable risk factors for first ischemic stroke were detected in six of 20 randomly selected subjects. Thus, a 30% prevalence rate was initially estimated. Allowing a maximum error of 5%, it was calculated that a sample size of 323 subjects was needed (Lwanga and Lemeshow, 1991). However, taking into account the probable non-compliance of the subjects to participate in the second examination, 500 subjects, 200 men and 300 women, without signs and symptoms of cerebrovascular disease, aged 50–79 years, were enrolled in the study. A systemic sample was used. Every third subject was selected from the official register, a complete list of all residents of the city. The first number of the sample was determined by selecting randomly. The randomly selected subjects, who consented to the study, were stratified into two age groups – 50–59 years and 60–79 years.

A structured standard questionnaire, which had previously been tested was used (Lechner and Hadjiev, 1998). The questionnaire included questions to confirm the presence or absence of stroke risk factors such as hypertension, cardiac diseases, cigarette smoking, diabetes mellitus, dyslipidemias, alcohol abuse, obesity, physical inactivity, elevated hematocrit, hyperuricemia, migraine, use of oral contraceptives, taking medication or following a diet and a family history of stroke in first-degree relatives. Cigarettes smoking was expressed as the average number of cigarettes currently smoked daily. Alcohol consumption was recorded as grams of ethanol per day. Physical activity was categorized as sedentary, moderate and heavy, according to the subjects’ response to the appropriate questions. Thorough physical, neurological and neurovascular examinations were carried out. Blood pressure was measured three times after a rest period in a sitting position and the values of systolic and diastolic blood pressure were averaged. Subjects who had a sustained blood pressure of 160/95 mmHg or more or received antihypertensive treatment were considered to have hypertension (WHO MONICA Project, 1997). ECG records were taken with 12 leads at rest. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m²). Fasting blood glucose concentration, hematocrit, plasma fibrinogen and blood lipids levels were also determined. The blood lipids fractions included total cholesterol (enzymatic colorimetric method), high-density lipoprotein (HDL) cholesterol (precipitation with phosphotungstic acid–MgCl₂ and enzymatic colorimetric determination of the cholesterol in the supernatant), low-density lipoprotein (LDL) cholesterol (precipitation with heparin and enzymatic colorimetric determination of the cholesterol in the supernatant) and triglycerides (enzymatic colorimetric method). Duplex scanning was performed to assess the degree of internal carotid artery stenosis, using SIM 7000 Challenge (Esaote Biomedica, Florence, Italy) with possibilities of bidimensional imaging, CW and PW Doppler. Duplex scans were performed and evaluated by an experienced and certified neurosonographer. A 7.5/5 MHz annular array probe with dynamic focusing was used. Peak systolic velocity and end diastolic velocity, spectrum broadening and pulsatility index were determined. According to Rockman et al. (1997) the degree of the internal carotid artery stenoses was defined as mild (< 50% diameter reduction – 0–49%), a peak systolic velocity < 140 cm/s), moderate (50–79%), a peak systolic velocity ≥140 cm/s and an end diastolic velocity 110–124 cm/s) and severe (80–99%), an end diastolic velocity ≥125 cm/s).

The modifiable vascular risk factors for first ischemic stroke (Sacco et al., 1997), which were considered in this study, are listed in Table 1.

The combination of three or more than three well-and less well-documented modifiable risk factors for first ischemic stroke was defined as multiple vascular risk factors.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Modifiable risk factors for ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertension</td>
<td>Systolic blood pressure, &gt;160 mmHg</td>
</tr>
<tr>
<td>2. Cardiac diseases</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>3. Cigarette smoking, &gt;20 cigarettes per day</td>
<td></td>
</tr>
<tr>
<td>4. Diabetes mellitus – fasting blood glucose, &gt;140 mg/dl (7.77 mmol/l)</td>
<td></td>
</tr>
<tr>
<td>5. Asymptomatic carotid stenosis of 50% or greater</td>
<td></td>
</tr>
<tr>
<td>6. Dyslipidemias</td>
<td>Total cholesterol, &gt;250 mg/dl (6.46 mmol/l)</td>
</tr>
<tr>
<td>7. Alcohol consumption, &gt;60 g ethanol per day</td>
<td></td>
</tr>
<tr>
<td>8. Physical inactivity – evaluated by questionnaire</td>
<td></td>
</tr>
<tr>
<td>9. Obesity – BMI (kg/m²)</td>
<td>Men, &gt;27.8</td>
</tr>
<tr>
<td>10. Hematocrit level</td>
<td>Men, &gt;54%</td>
</tr>
<tr>
<td>11. Fibrinogen, &gt;4.0 g/l</td>
<td></td>
</tr>
</tbody>
</table>
A second examination was performed after a 2-year follow-up. The response rate in the follow-up survey was 83.6% (418/500). Despite the telephone contacts, the remainder refused to participate in the study. The demographic distribution and baseline characteristics of the vascular risk factors between the subjects who were not followed up and the responders were not substantially different. The end points of the study were: transient ischemic attacks (TIAs), ischemic stroke (IS) and myocardial infarction. TIAs and IS were diagnosed on the basis of accepted clinical criteria. TIAs have been defined as brief episodes of focal loss of brain function, lasting less than 24 h (Special report from the NINDS, 1990).

During the follow-up period, treatment of the underlying risk factors with anti-hypertensive, blood glucose-lowering drugs, aspirin and appropriate dietary regimens was continued.

The examinations were performed with the patients' informed consent.

Statistical analysis was carried out using SPSS 8.0.0 (SPSS Inc., Chicago, IL, USA). The following analyses were used: frequency distribution, descriptive statistics, chi-squared test, Fisher's exact test and t-test. An age- and sex-adjusted conditional regression was performed to estimate the odds ratio and 95% confidential interval associated with each vascular risk factor. An outcome (TIAs, IS and myocardial infarction, taken together) was fitted as a dependent variable. The separate vascular risk factors (Table 1) and all their pairs were fitted as independent variables.

Results

The proportions of modifiable vascular risk factors among the subjects, included in the study are given in Table 2.

Three or more vascular risk factors have been detected in 52% (260/500) of the subjects examined (95% CI, 47.61–56.39%). Age and sex differences in the frequency of the multiple vascular risk factors were not found.

The frequency of various risk factors among the subjects with multiple vascular risk factors is shown in Fig. 1.

High LDL cholesterol concentration (78.1%), hypertension (65.8%), obesity (58.3%), cigarette smoking (41.9%) and cardiac diseases (39.6%) are the most frequent risk factors for ischemic stroke among persons with multiple vascular risk factors. Less frequent risk factors in this group of volunteers are hypercholesterolemia (24.7%), hypertriglyceridemia (23.2%), decreased HDL cholesterol (21.5%), physical inactivity (18.1%), increased fibrinogen level (11.7%), diabetes mellitus (8.8%), ACS of 50% or greater (8.8%), alcohol abuse (6.9%) and increased hematocrit level (1.5%).

After a 2-year follow-up, 2.7% (7/260) of the responders with multiple vascular risk factors reached an outcome end point.

The frequency of individual vascular risk factors among subjects with multiple risk factors, who have reached an outcome end point, is shown in Fig. 2.

The proportions of hypertension (85.7%), cardiac diseases (71.4%), ACS of 50% or greater (28.6%) and alcohol abuse (28.6%) are markedly increased among the cases, who have reached an outcome end point.

Using a conditional regression analysis, the relationships of the different modifiable vascular risk factors with the occurrence of ischemic events among the subjects enrolled in the study were determined. In age- and sex-adjusted conditional regression analysis the following combinations of vascular risk factors were significantly associated with the outcome end points of the study: hypertension and cardiac diseases (OR = 6.82; 95% CI, 1.21–8.41; P = 0.0293); cardiac diseases and obesity (OR = 6.13; 95% CI, 1.27–29.72; P = 0.0243); ACS of 50% or greater and high LDL cholesterol levels (OR = 11.11; 95% CI, 1.58–78.29; P = 0.0156).

Discussion

Previous studies have reported that the presence of certain multiple vascular risk factors increases the probability of stroke (Kannel, 1976; Wolf et al., 1991; Sacco et al., 1997) and the validity of a stroke probability point system based on Framingham profile, although partly, was proved by Copenhagen City Heart Study (Truelsen et al., 1994).

This population-based longitudinal epidemiological survey has focused on the prevalence rate and the distribution patterns of multiple risk factors for ischemic stroke. Similar data have not been reported so far. Three or more than three well- and less well-documented modifiable risk factors for first ischemic stroke have been detected in 52% (260/500) of the study subjects.
Dyslipidemias, hypertension, obesity, current cigarette smoking and cardiac diseases were found to be the most prevalent single vascular risk factors among the subjects with multiple vascular risk factors. ACS of 50% or greater is often relatively associated with other vascular risk factors. It occurred in 8.8% of the persons with multiple vascular risk factors, whereas its prevalence among the whole population is 6.4% (Mineva et al., 2002).

Hypertension, cardiac diseases, high LDL cholesterol level, obesity, cigarette smoking, ACS, decreased HDL cholesterol level and alcohol abuse are the most common risk factors among the subjects, who reached an outcome end point. However, because of the small number of the persons and the short follow-up period, these data could not be discussed in detail. Nevertheless, it should be pointed out that the lifestyle-associated risk factors – obesity, cigarette smoking and heavy alcohol consumption – are common among the persons who had reached an outcome end point.

These findings suggest that the presence of multiple vascular risk factors could shed light on the coexistence of multiple potential causes of ischemic stroke, which has recently been discussed (Barnett et al., 2000; Caplan, 2000; Moncayo et al., 2000). The high prevalence and importance of multiple modifiable vascular risk factors also suggests the need for relevant multimodality programmes for stroke prevention. It is generally accepted, that hypertension is the most important modifiable risk factor for stroke and has the highest population-attributable risk for stroke (Wolf, 1993; Gorelick, 1995). In an overview of 17 randomized controlled trials of hypertension a 38% reduction of stroke incidence has been found (Chalmers et al., 2000). Antihypertensive treatment is also effective and safe in elderly persons with isolated systolic hypertension; a 36% reduction in stroke incidence has been reported (Staessen et al., 1997). However, it is known that at any blood pressure level the risk of stroke depends on the associated risk factors (Kannel, 1976). Hypertension is usually combined with other risk factors and rarely, < 20%, occurs in isolation (Kannel, 2000). In hypertensives, who are current smokers or have ischemic heart disease, obesity or diabetes mellitus, the risk of stroke is markedly increased compared with controls (Du et al., 2000). That is why antihypertensive treatment only may fail to prevent stroke.
Despite the small study sample and the short follow-up period, the data indicate that besides hypertension, cardiac diseases, dyslipidemias and ACS, the lifestyle-associated risk factors contribute to the occurrence of cerebral ischemic events. It has also been reported that certain lifestyle-associated factors – recent heavy alcohol drinking and current cigarette smoking, seem to be independent risk factors for acute brain infarction (Haapaniemi et al., 1997).

In addition, several studies suggest that the modification of the preventable lifestyle-associated risk factors – cigarette smoking, alcohol abuse, physical inactivity and dietary regimes may reduce stroke incidence (Gorelick et al., 1999). It has also been shown that the intervention on all vascular risk factors may be more effective in reducing the stroke mortality than the treatment of only one or two risk factor abnormalities (Vartiainen et al., 1995).

In conclusion, the identification of persons with multiple vascular risk factors would allow their selection for primary medical or surgical stroke prevention. It is also becoming clear that multimodality stroke prevention can be more effective than controlling of only one vascular risk factor. However, additional studies are necessary to clarify the geographic and race-ethnic differences in the distribution patterns of multiple modifiable risk factors for stroke and their impact on subsequent cerebral ischemic events.

Acknowledgements

The authors wish to express their appreciation to Prof. Philip B. Gorelick, MD, MPH, Center for Stroke Research, RUSH Medical Center, Chicago, Illinois for his review of the manuscript and helpful suggestions.

References


Goldstein LB, Adams R, Becker K et al. (2001). AHA scientific statement. Primary prevention of ischemic stroke: a state-


