Thrombosis Research 165 (2018) 33–37

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Cancer-associated ischemic stroke: A retrospective multicentre cohort study

Stefano Grazioli[a,*], Maurizio Paciaroni[b], Giancarlo Agnelli[b], Monica Acciarresi[b], Andrea Alberti[b], Cataldo D'Amore[b], Valeria Caso[b], Michele Venti[b], Luigina Guasti[c], Walter Ageno[c], Alessandro Squizzato[c]

[a] Internal Medicine, Ospedale S.Antonio Abate, ASST Valle Olona, Gallarate, Italy
[b] Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Italy
[c] Research Center on Thromboembolic Disorders and Antithrombotic Therapies, Department of Medicine and Surgery, University of Insubria, Varese, Italy

ARTICLE INFO

Keywords:
Ischemic stroke
Cancer

ABSTRACT

Background: The association between stroke and cancer is well-known but insufficiently investigated. Aim of this multicentre retrospective cohort study was to estimate the prevalence of cancer-associated ischemic stroke, describe clinical outcomes in patients with cancer-associated ischemic stroke and investigate independent factors associated with active cancer.

Methods: Consecutive adult patients admitted for acute ischemic stroke were included. Included patients were admitted in the Stroke Unit of the Hospital of Perugia, Italy, from March 2005 to March 2015, and in a medical unit of the Hospital of Varese, Italy, from January 2010 till December 2011. Clinical and laboratory data of patients with and without active cancer were collected. Multivariate logistic regression analysis was performed to identify independent factors associated with active cancer.

Results: A total of 2209 patients admitted with acute ischemic stroke were included with a median hospital stay of 9 days (interquartile range 5.75–14). Mean age was 72.7 years (standard deviation +/− 13); 55% patients were male and 4.4% had active cancer. Factors significantly associated with the presence of active cancer were age > 65 years (odds ratio [OR] 3.34; 95% confidence interval [CI] 1.64–6.81), occurrence of venous thromboembolism [VTE] (OR 2.84; 95% CI 1.12–7.19), low-density lipoprotein (LDL) cholesterol level < 70 mg/dL (OR 1.92; 95% CI 1.06–3.47), cryptogenic stroke subtype (OR 1.93; 95% CI 1.22–3.04). Overall mortality rate during hospital stay was greater in patients with active cancer (21.5% vs. 10% $P < 0.05$).

Conclusions: Older age, occurrence of VTE, low LDL level, and cryptogenic stroke subtype, are independently associated with active cancer. Overall, our findings suggest a possible prevalent role of hypercoagulability in the pathogenesis of cancer-associated ischemic stroke.

1. Introduction

Cancer and cerebrovascular disease are major causes of morbidity and mortality and their association is well-known: an autopsy-based study of patients with known cancer has reported a 15% prevalence of cerebral infarction, only half of which were symptomatic [1] However, only few studies have extensively investigated the potential underlying mechanisms. These include traditional cardiovascular risk factors and cancer-related risk factors. Some authors reported atherosclerosis as the most common cause of cancer-associated stroke [1–2], but an hypercoagulable state may be present in several cancer patients, such as those receiving chemotherapy and hormone therapy [3–4]. Indeed, nonbacterial thrombotic endocarditis is a well-known hypercoagulability-associated mechanism of ischemic stroke in cancer patients [2–5].

Some studies have tried to identify differences between stroke patients with and without active cancer. Cryptogenic stroke, the presence of multiple embolic events on neuroimaging, D-dimer elevation, and concomitant venous thromboembolic events (VTE) were more frequently reported in cancer-associated ischemic stroke [5,6–9].

Published evidence on the presence of traditional cardiovascular risk factors is controversial: some studies showed no difference in their prevalence between stroke patients with cancer and without cancer [2−10]; conversely, other studies reported a lower incidence of these risk factors in the cancer group [11−12].

Therefore, we performed a large retrospective cohort study of patients admitted with acute ischemic stroke with the aim to: i) estimate the prevalence of cancer-associated ischemic stroke, ii) describe clinical

* Corresponding author at: U.O. Medicina, ASST Valle Olona, Ospedale S. Antonio Abate, Via Pastori, 4, 21013 Gallarate, Italy.
E-mail address: stefano.grazioli@pec.omceova.it (S. Grazioli).

https://doi.org/10.1016/j.thromres.2018.03.011
Received 17 December 2017; Received in revised form 7 March 2018; Accepted 13 March 2018
Available online 15 March 2018

outcomes in patients with cancer-associated ischemic stroke, iii) investigate independent factors associated with active cancer.

2. Methods

This study was designed as a retrospective cohort study.

2.1. Inclusion and exclusion criteria

Consecutive adult patients, of any age, gender and race, admitted for acute ischemic stroke at each participating center were included. According to World Health Organization [WHO] definition, acute ischemic stroke was defined by a combination of neuroimaging (cerebral computed tomography or magnetic resonance) and clinical criteria [13]. Ischemic stroke was defined as acute if occurred within 24 h prior to hospital admission. Included patients were admitted in the Stroke Unit of the Hospital of Perugia, Italy, from March 2005 to March 2015, and in a medical unit of the Hospital of Varese, Italy, from January 2010 till December 2011. All patients enrolled in Perugia were recruited using the database of an ongoing registry (Perugia Stroke Registry) [14]. Patients enrolled in Varese were identified using discharge codes according to the 9th Clinical Modification International Classification of Diseases (ICD-9-CM codes for ischemic stroke 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91). Charts of all eligible patients were retrieved for detailed evaluation.

2.2. Data extraction

Trained personnel retrospectively recorded information on age, gender and medical history, risk factors for ischemic stroke, i.e. atrial fibrillation (AF), diabetes mellitus (DM), arterial hypertension, hyperlipidemia, history of coronary heart disease (CAD), history of peripheral artery disease (PAD), history of ischemic stroke, history of transient ischemic attack (TIA), obesity, smoking, alcohol abuse. Data on total and low-density lipoprotein (LDL) cholesterol, triglycerides (TGL) and blood cell count, in particular platelet (PLT), were also collected.

Hypertension was defined as the history of hypertension or the use of antihypertensive drugs. Hyperlipidemia was defined as the use of cholesterol-lowering therapy, a fasting total serum cholesterol level ≥ 220 mg/dL, a triglyceride level ≥ 175 mg/dL, or a LDL cholesterol level ≥ 130 mg/dL. We also analysed LDL cholesterol level ≤ 70 mg/dL, the European target for cardiovascular prevention in very high-risk patients [15].

DM was defined as a fasting blood glucose level ≥ 126 mg/dL, a glycosylated hemoglobin A1c concentration ≥ 6.5%, or the use of a drug for diabetes. Obesity was defined as body mass index (BMI) > 30. Smoking was defined as current smoking or past history of > 5 cigarettes per day. Alcohol abuse was defined as ≥ 300 g per week. AF was diagnosed with an electrocardiogram.

The subtype of ischemic stroke was classified according to Trial Org 10,172 in Acute Stroke Treatment (TOAST trial) criteria as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, stroke of undetermined etiology [16].

Additional data were also collected on previous treatments, in particular antiplatelet drugs, hormones, and statin use, and on revascularization therapies for ischemic stroke. Stroke severity was evaluated with the National Institute of Health Stroke Scale (NIHSS). The presence of concomitant symptomatic VTE (i.e. proximal deep venous thrombosis [DVT] and pulmonary embolism [PE]) during hospital stay was collected if objectively diagnosed by an imaging test, i.e. ultrasonography for DVT, and computed tomography pulmonary angiography or perfusion lung scan for PE.

Cancer-associated ischemic stroke was defined as an acute cerebrovascular event occurring in a patient with an active cancer. Active cancer was defined as a diagnosis of cancer or any treatment for cancer within 6 months the occurrence of ischemic stroke, or a concomitant metastatic cancer [17]. Occult cancer was no systematically searched with a formal diagnostic work-up in any centre. Data related to cancer site were also recorded. Finally, mortality during hospital stay was recorded.

2.3. Statistical analysis

Categorical variables were expressed as number and percent. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normal distribution of the data.

Odds ratio (OR) and 95% confidence interval (CI) for risk factors associated with cancer were estimated using logistic regression. Any variable with a p value < 0.2 at univariate analysis was included in a multivariate model. At the multivariate analysis, variables with a p value < 0.05 were considered statistically significant.

Statistical analysis was performed with the use of SPSS 20.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 2209 patients admitted with an acute ischemic stroke were included, 1790 patients in Perugia and 419 patients in Varese. Overall mean age was 72.7 years (SD +/− 13), ranging from 21 to 100 years; 1230 (55%) patients were male. Median hospital stay was 9 days (IQR] 5.75–14), including also patients who died during hospitalization.

Baseline characteristics are reported in Table 1 and in Table S1 (in the Appendix). In particular, 300 (13.5%) patients had a previous stroke, 86 (3.8%) a previous TIA, and 319 (14.3%) had concomitant CAD. In 866 (38.9%) patients, ischemic stroke occurred while on antiplatelet therapy, and 51 (2.3%) patients had VTE during hospitalization. Patients enrolled in Varese were significantly older, had more cryptogenic stroke subtype and more rate of active cancer, and received less revascularization therapy for ischemic stroke in comparison to patients enrolled in Perugia (see Table S1 in the Appendix).

Cancer was present in 98 patients (4.4%), either known (n = 95) or diagnosed during hospitalization (n = 3) (see Table 2). Ten cancer patients were taking hormonal therapy at the time of diagnosis. Four patients had essential thrombocythemia (ET). Patients with active cancer were older (mean age 76.8 vs. 72.7 years P < 0.05), had more cryptogenic stroke subtype (31.6% vs. 20.4% P < 0.05), and a higher incidence of VTE diagnosis during hospitalization (5.8% vs. 2.1% P < 0.05) than patients without active cancer. Patients with active cancer had fewer cardiovascular risk factors than patients without active cancer: diabetes mellitus (14.7% vs. 25.5%; P < 0.05), LDL cholesterol level < 70 mg/dL (15.3% vs. 8.4% P < 0.05), LDL cholesterol level > 130 mg/dL (14.7% vs. 25.5%P < 0.05) and triglyceride level > 175 mg (6.8% vs. 14.3% P < 0.05).

Information on smoking habit and alcohol consumption was available only for patients enrolled in Perugia (n = 1790): 466 (25.9%) patients were smokers, 9 (13.3%) among patients with active cancer; 56 (3.1%) patients were alcohol abusers, 1 (1.5%) patient among those with active cancer.

At multivariate logistic regression analysis (see Table 3), the following variables were significantly associated with active cancer: age > 65 years (OR 3.34; 95% CI 1.64–6.81); concomitant VTE (OR 2.84; 95% CI 1.12–7.19), LDL cholesterol level < 70 mg/dL (OR 1.92; 95% CI 1.06–3.47), and cryptogenic stroke subtype (OR 1.93; 95% CI 1.22–3.04). Diabetes mellitus was at the limit of statistical significance (OR 0.56; 95% CI 0.31–1.00). After excluding patients with ET, the following variables were confirmed to be significantly associated with active cancer at multivariate logistic regression analysis (see Table S2 in the Appendix): age > 65 years (OR 3.21; 95% CI 1.57–6.57); concomitant VTE (OR 3.03; 95% CI 1.20–7.64), LDL cholesterol level <