The Activity of Malignancy May Determine Stroke Pattern in Cancer Patients

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Background: It has been suggested that stroke in patients with cancer may differ from the conventional pattern. The aim of this study was to evaluate the burden of vascular risk factors, stroke etiology, and short-term outcome in patients with active and nonactive malignancy compared with patients without cancer. *Methods:* This is a prospective cohort study of consecutive acute stroke patients admitted to our department between September 2006 and September 2011. We distinguished between the following: (1) patients with active malignancy (AM, diagnosed not earlier than 12 months before stroke); (2) patients with nonactive malignancy (non-AM); and (3) cancer-free (CF) patients, used as a reference. *Results:* Pre-existing cancer was found in 90 of 1558 patients, including 41 (2.6%) cases with AM and 49 (3.1%) cases with non-AM. Compared with CF patients, AM patients less frequently had a history of previous stroke (2.4% versus 17.9%, $P = .018$) and more frequently experienced ischemic strokes of undetermined etiology (62.5% versus 38.3%, $P = .002$). Non-AM patients did not differ in the distribution of vascular risk factors but more often experienced stroke caused by small vessel occlusion (20.0% versus 8.0%, $P = .004$). Inflammatory blood markers were elevated especially in patients with AM. Short-term prognosis was similar across all groups. *Conclusions:* Stroke pattern in patients with non-AM appears very similar to that observed in the CF patients. However, our findings support the thesis that cancer-specific prothrombotic mechanisms play an important role in stroke patients with AM, which may be related to active inflammatory and immune processes. Malignancy does not influence short-term prognosis of stroke. **Key Words:** Etiology—malignancy—outcome—prothrombotic—risk factors—stroke.

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Stroke and cancer are common causes of worldwide mortality and morbidity. Because of the aging of population, burden of these 2 diseases is projected to steadily increase over the next decades. Considering the development of diagnostic and therapeutic strategies for cancer, the survival of oncological patients has also improved. Therefore, the issue of stroke incidence and prognosis among cancer patients is a matter of increasing interest.[1,2]

The discussion about relationships between stroke and cancer has been initiated by Graus et al[3] who reported that stroke may be an important complication of cancer. Some authors support the thesis of causal association between cancer and stroke,[3-7] whereas others consider it a simple coincidence.[8-12] Studies addressing the issue of cancer and stroke were methodologically heterogeneous.

Oncologists tended to analyze incidence of stroke among patients with cancer,[3,9] whereas neurologists concentrated on stroke pattern among unselected patients with positive history of cancer or patients with active malignancy.[4,6-8,10-12] However, none of the previous studies distinguished between active and nonactive cancer in a single cohort.

The aim of the present study was to evaluate the stroke pattern and short-term outcome in patients with active or nonactive malignancy in comparison with patients without cancer.

Material and Methods

This is a prospective cohort study of consecutive acute stroke patients admitted to our Department of Neurology between September 2006 and September 2011. The Department provides neurologic care for approximately 250,000 inhabitants of a highly urbanized area (Warsaw, Poland) with an annual volume of approximately 300 stroke cases. The diagnosis of ischemic stroke or intracerebral hemorrhage was made according to the World Health Organization criteria and supported with brain imaging (computed tomography or magnetic resonance imaging). Intravenous thrombolysis was administered according to the Safe Implementation of Thrombolysis in Stroke protocol.[13]

Data were prospectively entered to a detailed stroke registry based on the National Institute of Neurological and Communicative Disorders and Stroke Data Bank protocol with minor modifications.[14] They included patients' demographics, comorbidities, routine laboratory findings, and the course of stroke. For the purpose of the present study, medical records were additionally checked, and patients were interviewed for the history of cancer. Information about the type of cancer, presence of metastases, and time between the diagnosis of cancer and the stroke onset was collected. Patients with primary brain tumors or cerebral metastases were not included in the analysis.

Patients were categorized into 3 nonoverlapping groups: (1) group with active malignancy (AM) that included patients with newly diagnosed cancer or with confirmed recurrent cancer and/or metastases within 12 months before stroke onset; (2) group with nonactive malignancy (non-AM) that included patients diagnosed with cancer more than 1 year before stroke; and (3) cancer-free (CF) group that was used as a reference. There is no consensus in the literature on the definition of active malignancy. Some authors used the criterion of 6-month delay between the diagnosis of cancer and index stroke,[4,6,7,15,16] whereas others considered cancer active if stroke occurred during oncological therapy.[17] Neurologic deficit was assessed with the National Institutes of Health Stroke Scale (NIHSS). The etiology of ischemic stroke was determined according to the criteria developed for the Trial of Org 10172 in Acute Stroke Treatment.[18] Clinical endpoints included the following: (1) good outcome at discharge (modified Rankin Scale score of 0-2 points, meaning alive and independent); (2) neurologic improvement at discharge (improvement of at least 4 points on the NIHSS from baseline or achieving an NIHSS score of 0); and (3) in-hospital mortality.

The study complies with the provisions of the Declaration of Helsinki and was approved by the local Ethics Committee. All participants gave their informed consent.

Statistical Analysis

Categorical variables were presented as a number of valid observations with ratio (%). Proportions were calculated with exclusion of missing values from the denominator. Continuous variables were presented as a median with interquartile range (IQR), as their distribution (determined using the Shapiro–Wilk test) was mostly not normal. Comparisons between both cancer-positive groups and the reference group of CF patients were made using the chi-square test or Mann–Whitney U test. If the expected value in at least 1 cell of a 2×2 contingency table was less than 5, Yates correction was applied. To minimize the risk of type I error, paired comparisons (AM versus CF and non-AM versus CF) were preceded by an overall chi-square test or Kruskal–Wallis test, as appropriate. A separate sensitivity analysis was carried out under assumption that the malignancy is active only if it was diagnosed within the last 6 months before the index stroke.

Calculations were carried out using the STATISTICA 10.0 software package (StatSoft Inc, Tulsa, OK). All tests were 2-tailed, and P less than .05 was considered significant.

Results

General Patient Characteristics

A total of 1558 stroke patients (722 men and 836 women) were included in the analysis. Ninety (5.8%) of them had a confirmed diagnosis of cancer. The most common cancer sites were breast, lung, and colon (Table 1). Forty-one cancer-positive patients (45.6%) were classified as having AM, and 49 cancer-positive patients (54.4%) were classified as having non-AM (Fig 1).

Vascular Risk Factors and Prestroke Patient Status

Patients with AM tended to be more often male (61.0% versus 46.1%, $P = .060$) and have a lower burden of atrial fibrillation (7.3% versus 23.5%, $P = .016$) than CF patients. They less frequently experienced previous stroke (2.4% versus 17.9%, $P = .018$) but tended to have more preexisting disability (43.9% versus 31.1%, $P = .083$; Table 2).

Patients with non-AM tended to be older than CF patients (77 versus 75 years, $P = .058$) and were more often