



BRAIN NEOPLASMS IN PATIENTS WITH CEREBROVASCULAR DISEASES

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ABSTRACT

There is recent evidence of co-occurrence of benign and malignant brain tumours and cerebrovascular disorders in the same patients. The present concise review analyzes the newly-published foreign literature on this actual topic. The epidemiological investigations reveal an association between the acute ischaemic and haemorrhagic stroke, on the one hand, and some common cerebral neoplasms, on the other hand. The role of modern thrombolytic therapy in such patients is outlined. The risks of chemotherapy and radiotherapy for the development of stroke should be taken into consideration. A series of interesting rare cases illustrating the diagnostic and therapeutic opportunities in the patients presenting with simultaneous or consecutive common cerebral neoplasms and stroke proves the necessity of careful diagnosis and timely management of these patients in the routine clinical practice.

Key words: ischaemic stroke, haemorrhagic stroke, multiform glioblastoma, meningioma, epidemiology, diagnosis, treatment, case reports

INTRODUCTION

Contemporary advances in the diagnosis, management and prevention of primary brain neoplasms and cerebrovascular disorders enable the identification of a rising number of patients in adulthood and childhood presenting consecutively or simultaneously with such diseases worldwide.

Cerebrovascular disease is the second leading cause of central nervous system pathology in cancer patients [1]. Cancer-associated hypercoagulation plays an important role in cancer-related stroke. Cancer, by conferring a hypercoagulable state, may lead to an ischaemic stroke [2]. Cancer-related stroke may have different phenotypes from non-cancer stroke, especially in terms of stroke progression and recurrence [3].

Epidemiology of stroke-associated brain tumours

A retrospective review of patients with primary brain tumours diagnosed with MRI-confirmed ischaemic stroke between 1996 and 2006 identifies sixty-eight cases in 66 patients [4]. The most common brain tumours are gliomas (in 60%), meningiomas (in 25%) and primary central nervous system lymphomas (in 6% of the cases). Ischemic stroke is the initial clinical diagnosis in only 43% of the patients. According to stroke etiology, the operative complications

prevail (in 49%) followed by cardioembolic and small vessel lacune (in 12% each), large vessel (in 6%), other (in 15%), and undetermined cause (in 7% of the cases).

Within a nationwide study, all 820491 individuals in Sweden with a diagnosis of cancer between 01. 01. 1987 and 31. 12. 2008 have been followed-up for first hospitalisation on the occasion of haemorrhagic or ischaemic stroke [5]. Stroke risk is highest during the first six months after diagnosis of cancer of the nervous system (CI 29; 25-34) for haemorrhagic stroke and (CI 4.1; 3.4-4.8) for ischaemic one.

Computer tomography (CT) is used to differentiate glioma stroke from simple cerebral haemorrhage in a total of 45 patients with glioma stroke and stroke as the initial symptom of the disease [6]. There are 25 patients with astrocytoma (in 55.56%), 11 with oligodendroglioma (in 24.44%), eight with ependymoma (in 17.78%), and one with multiform glioblastoma (in 2.22% of the cases). The coexistence of haemorrhage and tumour signs is the major CT manifestation.

Stroke has been diagnosed in five children with brain tumours among 1411 children with cancer at a mean of five months after cancer diagnosis [7]. Haemorrhagic and ischaemic strokes occur with approximately equal frequency in this contingent.

Thrombolysis in stroke and brain neoplasms

Of the 124083 thrombolysis-treated stroke patients identified from the 2002-2011 USA Nationwide Inpatient Sample, 416 (0.34%) present with brain tumours [8]. Inpatient mortality (OR 0.98; 95% CI 0.77-1.26, $p=0.918$), rate of home discharge (OR 1.15; 95% CI 0.87-1.53, $p=0.40$) and rate of intracranial haemorrhage (OR 0.94; 95% CI 0.62-1.44, $p=0.801$) are similar between brain tumour-associated strokes and non-brain tumour-associated ones. Compared to non-brain tumour-associated strokes, malignant primary brain tumour-associated ones are independently related to higher in-hospital mortality rate (OR 2.51; 95% CI 1.66-3.79, $p<0.001$), lower home discharge (OR 0.36, 95% CI 0.18-0.72, $p=0.004$), and increased risk of intracranial haemorrhage (OR 2.33, 95% CI 1.49-3.65, $p<0.001$). Among the brain tumour-associated strokes, intraparenchymal tumour location is related to higher mortality rate (OR 2.51; 95% CI 1.20-5.23, $p=0.014$) and lower home discharge (OR 0.26; 95% CI 0.13-0.53, $p<0.001$).

The systematic literature search in *MEDLINE* and *GoggleScholar* during the period from 1990 to 2012 reveals

12 patients with cerebral neoplasms on thrombolysis for different reasons [9]. The intracerebral haemorrhage occurs in one patient with a glioblastoma. The authors report one new case of a 71-year-old patient with a large right frontal meningioma who has fully recovered with thrombolysis from a severe acute ischaemic stroke.

Chemotherapy and radiotherapy in stroke and brain neoplasms

A total of 3812 patients undergoing elective cranial surgery for a primary or secondary brain tumour obtained from the American College of Surgeons National Surgical Quality Improvement Program database between 2006 and 2012 have been analyzed [10]. Of them, 152 patients have been on concurrent neoadjuvant chemotherapy. Their complication rate is 23.68% while that of the rest patients is lower (17.65%; $p=0.057$). The multivariable regression analysis indicates that the patients on neoadjuvant chemotherapy present with significantly increased odds ratios (OR) of developing a stroke with neurological deficit [OR 3.39; 95% confidence interval (CI) 1.37-8.40], all-cause postoperative morbidity rate (OR 1.57; 95% CI 1.04-2.37), and mortality rate following surgery (OR 3.81; 95% CI 1.81-8.02) than the control patients.

Within a retrospective study of recurrent malignant glioma patients while on antiangiogenic therapy with bevacizumab, a monoclonal antibody against vascular endothelial growth factor, between 2005 and 2010 at the National Cancer Institute, USA, eight patients develop radiographically-confirmed ischaemic stroke and 14 patients experience intracranial haemorrhage [11]. The patients with ischaemic stroke are treated with antiangiogenic agents longer than those with intracranial haemorrhage (median, 16.2 versus 2.6 months, $p=0.001$). The median survival is 7.8 months and 2.6 months, respectively.

Out of 431 patients aged up to 21 years with a primary brain tumour, 14 present with 19 events of stroke or transient ischaemic attack during a median follow-up of 6.3 years [12]. Overall, 61.5% of the children receive radiation therapy, including 13 of 14 children with events. The median time from the first radiation therapy procedure to the first event is 4.9 years. For any brain irradiation, the stroke/transient ischaemic attack hazard ratio (HR) is 8.0 (95% CI, 1.05-62; $p=0.045$); for the circle of Willis, irradiation HR is 9.0 (95% CI, 1.2-70; $p=0.035$), and for focal non-circle of Willis, it is 3.4 (95% CI, 0.21-55; $p=0.38$). Therefore, the cranial irradiation is an important risk factor for stroke or transient ischaemic attack in children with brain tumours.

The risk of cerebrovascular accidents and secondary brain tumours after surgery or radiotherapy in 143 patients with a pituitary adenoma diagnosed between 1993 and 2000 has been assessed during a mean follow-up of 15.5 years [13]. In univariate analysis, age >60 years (HR 11.93; 95% CI 6.26-23.03; $p<0.001$), male sex (HR 3.67; 95% CI 2.03-6.84; $p<0.001$), and reirradiation (HR 3.41; 95% CI 1.05-9.68; $p=0.04$) are related to worse cerebrovascular accident-free survival. In multivariate analysis, only age >60 years relates with such a survival. Two patients develop a secondary brain tumour following either surgery, or radiotherapy.

CASE REPORTS

Recently, numerous rare cases reports dealing with the co-occurrence of acute stroke and cerebral neoplasms have been published.

The intravenous recombinant tissue plasminogen activator has been administered in two acute ischaemic stroke patients with extraparenchymal intracranial neoplasms observed on neuroimaging prior to treatment [14]. It deals with an acoustic schwannoma and a falcine meningioma. There is no intratumoural haemorrhage as of at least one week following treatment. A rare case of a successful intravenous thrombolysis with recombinant tissue plasminogen activator for acute ischaemic stroke in a patient with oligodendroglioma on bevacizumab therapy without any haemorrhagic complications has been reported [15].

A case of a 78-year-old male patient with acute ischaemic stroke and intracranial meningioma has been described [16]. Alteplase, a recombinant tissue plasminogen activator, has successfully been administered in a dosis of 0.3 mg/kg for intraarterial thrombolysis. An Italian patient with ischaemic stroke and subsequent partial haemorrhagic transformation which is related to a small-sized tuberculum sellae meningioma has been described [17].

A 31-year-old male patient with an extremely rare case of small meningotheial meningioma related to an acute ischemic stroke and preceded by recurrent transient ischemic attacks has been reported [18]. Magnetic resonance imaging reveals acute cerebral infarction in the right frontal lobe and a tumour of 20 mm in size in the planum sphenoidale encasing the right anterior cerebral artery. Cerebral angiography demonstrates occlusion of the right A(2) portion. A rare case of a 30-year-old right-handed female patient with cerebral infarction due to a sphenoid wing meningotheial meningioma (with progesterone receptor positivity) leading to an occlusion of the middle cerebral artery one month after childbirth has been reported [19]. A silent meningioma leading to stroke, following coronary artery bypass grafting in a 62-year-old patient as an unusual cause of cerebral dysfunction has been described [20].

A case of temporal lobe glioblastoma with a rare presentation as an acute ischaemic stroke has been reported [21]. A 77-year-old woman presents with sudden onset of left hemiparesis and hemihypoesthesia. The neuroradiological studies reveal an acute ischaemic lesion in the right lenticulostriate artery territory and a right anterior temporal lobe tumour, enhancing heterogeneously after contrast with enhancement of the right middle cerebral artery wall. The histopathological analysis of the resected temporal lesion demonstrates a multiform glioblastoma with tumoural infiltration of the vascular wall.

A rare case of a 58-year-old female patient with surgically removed left frontotemporal multiform glioblastoma and ischaemic stroke in the territory of the middle cerebral artery has been reported [22]. Postoperatively, due to the increasing stroke area and worsening patient's clinical status, urgent decompressive craniectomy has been carried out followed by effective radiation therapy and chemotherapy.

A case with single instances of haemorrhagic stroke and subsequent glioblastoma that are temporally separated

by several years has been presented [23]. The recent findings in the mechanisms of brain repair and tumour biology are illustrated.

A case of cerebellar glioblastoma presenting with clinical and imaging features of posterior circulation stroke [24] as well as a patient who has developed glioblastoma two years after an ischaemic stroke in the territory of the middle cerebral artery have been reported [25].

A 47-year-old male patient presenting first with hypertensive haemorrhagic thalamic stroke has been described [26]. The rapid patient's deterioration four months later requires a biopsy examination that displays an anaplastic astrocytoma. Misdiagnosis of tumour as stroke can occur in patients with vascular risk factors who do not have a previous history of neoplasia.

Dynamics of world publication output

In October, 2015, we performed a retrospective search of scientific publications relevant to the topic of brain neoplasms related to cerebrovascular diseases which have primarily been published in 2000-2014 and then abstracted in *Scopus* data-base (the Netherlands). There were a total of 1608 papers in 19 languages by authors from 66 coun-

tries from the whole world. There were 1423 English-language papers which significantly dominated like in most scientometric distributions. Far behind followed the publications in French, Spanish, Japanese, German, and Chinese which amounted to 36, 36, 34, 20, and 19, respectively. There were 1019 original articles, 476 review articles, 43 conference papers, 22 letters-to-the-editor, 19 editorials, 9 short surveys, 5 book chapters, etc.

The permanent growth of the publication activity worldwide was illustrated on Fig. No 1 while the distribution of some countries according to the number of the publications by their authors was demonstrated on Fig. No 2. The scientists from the USA presented with a total of 585 papers abstracted in *Scopus* during this 15-year period.

The most important journals, the so-called 'core' journals on this topic were listed in Table No 1. They should be attractive for the Bulgarian scientific community, too.

In **conclusion**, because of the sociomedical importance of the acute cerebrovascular diseases and common brain tumours their association in one and the same patient should obligatorily be taken into consideration in everyday outpatient and hospital neurological practice.

Fig. 1. Annual dynamics of relevant publications abstracted in *Scopus* in 2000-2014



Fig. 2. Country distribution according to abstracted publications count



Table 1. ‘Core’ journals in the field of brain neoplasms and cerebrovascular diseases

No	Title	Country	Papers
1.	<i>Stroke</i>	USA	32
2.	<i>Neurosurgery</i>	USA	31
3.	<i>Journal of Neurosurgery</i>	USA	27
4.	<i>Neurology</i>	USA	24
5.	<i>Journal of Neuro Oncology</i>	USA	22
6.	<i>American Journal of Neuroradiology</i>	USA	19
7.	<i>Journal of Cerebral Blood Flow and Metabolism</i>	USA	17
8.	<i>Neuroradiology</i>	Germany	16
Total		n=188	
		11.69%	

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