Affective Symptoms and White Matter Changes in Brain Tumor Patients

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BACKGROUND: **Affective symptoms are frequent in patients with brain tumors. The origin of such symptoms is unknown; either focal brain injury or reactive emotional distress may be responsible. This cross-sectional pilot study linked depressive symptoms and anxiety to white matter integrity. The objective was to test the hypothesis of a relationship between tissue damage and brain function in patients with brain tumors and to provide a basis for further studies in this field.**

METHODS: **Diffusion tensor imaging was performed in 39 patients with newly diagnosed supratentorial primary brain tumor. Patients completed the Beck Depression Inventory, and examiners rated them on the Hamilton Depression Rating Scale (HDRS). State and trait anxiety were measured using the State-Trait Anxiety Inventory. Correlations between fractional anisotropy (FA) and psychological measures were assessed on the basis of regions of interest; the defined regions of interest corresponded to clearly specified white matter tracts.**

RESULTS: **Statistical analysis revealed correlations between FA in the left internal capsule and scores on the HDRS, Beck Depression Inventory, and State-Trait Anxiety Inventory ($P < 0.05$). HDRS scores were also correlated with FA in the right medial uncinate fasciculus, and state anxiety scores were significantly correlated with FA in the left lateral and medial uncinate fasciculus ($P < 0.05$).**

CONCLUSIONS: **Our results suggest that neurobiologic mechanisms related to the integrity of tissue in specific white matter tracts may influence affective symptoms in patients with brain tumors, and these mechanisms can be investigated with diffusion tensor imaging. However, prospective observational studies are needed to investigate further the links between brain structures and the severity of affective symptoms in this patient population.**

INTRODUCTION

Affective symptoms are frequent in patients with brain tumors. The reported prevalence of clinically significant depressive symptoms in patients with brain tumors is 15%–44% (1, 18, 24, 33). Symptoms of anxiety are even more common, affecting 62% of patients with primary brain tumor before surgery (7, 20, 26). It has been shown that depression is associated with medical complications and lower survival rates (9, 17, 18). Patients with brain tumors who are depressed also have a lower quality of life than patients who are not depressed (19). The occurrence of psychological symptoms in patients with brain tumors is well documented, but their origin remains obscure. Symptoms may be due to focal brain injury arising from the tumor and accompanying edema or to more diffuse neural damage caused by radiation therapy, toxic medication or high-dose corticosteroid therapy; however reactive emotional distress and social or family problems may also cause severe affective symptoms. A better understanding of the processes underlying depressive symptoms and anxiety in patients with a brain tumor may lead to more effective treatment, better quality of life for patients, and perhaps better outcomes.

There is clear evidence that depressive symptoms and anxiety are linked to dysfunction in neuronal networks involved in

Key words
- Anxiety
- Depression
- Diffusion tensor imaging
- Internal capsule
- Primary brain tumor
- Uncinate fasciculus

Abbreviations and Acronyms
BDI-A1: Beck Depression Inventory
DTI: Diffusion tensor imaging
FA: Fractional anisotropy
HDRS: Hamilton Depression Rating Scale
MRI: Magnetic resonance imaging
STAI-G: State Trait Anxiety Inventory (German version)
ROI: Region of interest
WM: White matter

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emotion. These networks comprise cortical midline structures (e.g., the medial orbitofrontal, prefrontal, and cingulate cortex) and subcortical limbic structures such as the striatum, thalamus, and amygdala (21, 25, 31).

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that can be used for evaluation of the microstructural integrity of brain tissue. More specifically, it can be used to assess the tissue integrity of white matter (WM) tracts. Fractional anisotropy (FA) is calculated as a measure of the directional preference of water diffusion to disentangle diffusion effects on image contrast. DTI is widely used in psychiatric neuroscience to reveal abnormal connectivity between core brain regions of neural networks linked to affective symptoms (10, 14, 37). Changes of the FA in different brain regions have been shown to be related to the severity of depressive symptoms (5, 8, 23).

The objective of this exploratory study was to investigate potential correlations between depressive symptoms and anxiety with alterations in WM in patients with brain tumors. We hypothesized that there would be alterations in FA that were dependent on the severity of affective symptoms in brain regions known to be involved in affective processing. This is the first study to our knowledge to investigate the links between psychological symptoms and structural connectivity in brain regions involved in emotional processing in a sample of patients with brain tumors. This pilot investigation is intended to provide a basis for further studies in this field to link information from neuroscience with the clinical appearance of affective symptoms in patients with brain tumors and, eventually, reveal new diagnostic and treatment strategies.

MATERIALS AND METHODS

Subjects

Between March 2009 and April 2010, 39 adult patients (21 men, 56.1 years old ± 17.0 [mean ± SD]) with a new diagnosis of supratentorial primary brain tumor were recruited from the Department of Neurosurgery at the University Hospital Zurich. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Zurich (project number E-70/2008). Informed consent was obtained from all patients before participation.

Demographic and Medical Data

Sociodemographic data—marital status (single, 28%; married, 62%; divorced, 5%; widowed, 5%), parenthood (yes, 41%), and occupation (employed, self-employed, or homemaker, 64%; student, 10%; disabled or retired, 26%)—were collected during admission to the hospital. Patients included in the study showed comorbidities such as neurologic disturbances (seizures [n = 24], other [n = 2]), cardiovascular disease (hypertension [n = 10], coronary disease [n = 1], heart rhythm disturbances [n = 3]), and metabolic disorders (diabetes [n = 3], dyslipidemia [n = 2], hyperthyroidism [n = 1]). Neuroradiologic diagnoses of brain tumor were made using MRI. Histologic grading after surgery was based on the World Health Organization classification (15). The presence of incomplete tumor removal was checked using contrast-enhanced MRI examination within 72 hours after surgery. Appropriate standardized combined modality therapy with temozolomide and radiation was administered according to the decision of our interdisciplinary neuro-oncology board. Temozolomide was administered in patients with glioblastoma (World Health Organization IV) with a postoperative Karnofsky index >60–70 (n = 13). Most patients with a diagnosis of anaplastic astrocytoma (World Health Organization III) received radiotherapy (n = 14; radiation dose, 51 Gy ± 12 [mean ± SD]). Medical details are shown in Table 1. Patients with a history of substance dependence were excluded from the study. A history of depressive mood before brain tumor diagnosis was reported by 5 patients, but no patient with preexisting generalized anxiety was included.

Assessment of Clinical and Behavioral Characteristics

Depressive symptoms were evaluated in 2 ways. Patients completed the Beck Depression Inventory (BDI-1A), and

Table 1. Histologic and Anatomic Characteristics of Tumors

Category	Characteristics
Postsurgical histopathologic classification (*n*)	
WHO I	13
WHO II	5
WHO III	7
WHO IV	12
Metastasis	2
Tumor size (mm)	
Range	14–90
Mean ± SD	45 ± 20
Tumor volume (mm^3)	
Range	8,789–140,995
Mean ± SD	37,856 ± 37,081
Edema volume (mm^3)	
Range	0–228,208
Mean ± SD	94,173 ± 92,638
Tumor lateralization (*n*)	
Left	20
Right	19
Tumor location (*n*)	
Frontal	15
Limbic system	9
Basal ganglia	2
Temporal	5
Parieto-occipital	8
Tumor removal (*n*)	
Complete	12
Incomplete	27

WHO, World Health Organization.