The effect of brain tumour laterality on anxiety levels among neurosurgical patients

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Objectives: The aim of this study was to investigate the level of anxiety in patients with a primary brain tumour and to analyse the effect of tumour laterality and histology on the level of anxiety. Recurrent measurements were assessed preoperatively, three months, and one year after operation.

Methods: The study population consisted of 101 patients with a primary brain tumour from unselected and homogeneous population in northern Finland. The patients were studied preoperatively with CT or MRI to determine the location of the tumour. The histology of the tumour was defined according to WHO classification. The level of anxiety was obtained by Crown-Crisp Experiential Index (CCEI) scale.

Results: The patients with a tumour in the right hemisphere had statistically significantly higher mean anxiety scores compared to the patients with a tumour in the left hemisphere before surgery of the tumour. By three months and by one year after surgical resection of the tumour, the level of anxiety declined in patients with a tumour in the right hemisphere. A corresponding decline was not found in patients with a tumour in the left hemisphere. According to laterality by tumour histology, the level of anxiety decreased significantly in male and female patients with a glioma in the right hemisphere, but a corresponding decline was not significant in the female patients with a meningioma in the right hemisphere. Decreased level of anxiety was not found in patients with gliomas or meningiomas in the left hemisphere by follow up measurements.

Conclusions: Primary brain tumour in right hemisphere is associated with anxiety symptoms. The laterality of anxiety seems to reflect the differentiation of the two hemispheres. The level of anxiety declined after operation of right tumour, approaching that of the general population. The effect of right hemisphere gliomas on anxiety symptoms deserves special attention in future research.

Several studies have focused on hemispheric lateralisation in neuropsychiatric disorders.^{1,2} Left brain damage has been found to be associated with depressive affective states,^{1,3–5} while apathy⁶ and mania¹ have been associated with right brain damage. Anxiety as a symptom of brain damage has not been as thoroughly studied as other psychiatric disorders,¹ but there is evidence of right cortical disturbance in patients with panic anxiety.⁷ Several case reports have described relationships between focal right sided brain lesions and anxiety or panic.^{8–11} By using a neurological stroke patient sample (n = 309), Castillo *et al*¹² suggested that anxiety combined with depression was associated with left cortical lesions, whereas anxiety alone was associated with right hemisphere lesions. Another study of healthy university students without any brain damage showed that depression and anxiety may be associated with opposing biases in perceptual asymmetry scores defined by neuropsychological tests; depression with left sided and anxiety with right sided.¹³ There have also been opposite findings, but these are based on case reports or small databases.^{14,15}

Only a few studies have been done on psychiatric symptoms in patients with a primary brain tumour, and most of our knowledge is a result of individual case reports and case series.^{8–11,15} However, there are two studies with a sophisticated study design and unbiased study sample suggesting a link between neuropsychiatric symptoms and tumour location.^{16,17} Pringle *et al*¹⁶ studied patients (n = 109) with solitary intracranial neoplasms and anxiety and depression before and after surgery, compared with control population. They found that before the operation 30% of patients were probably anxious, 19% were possibly anxious, and 51% had scores suggesting no significant anxiety measured by Hospital Anxiety and Depression Scale (HAD). In preoperative assessments, female patients with a left sided tumour had higher levels of anxiety than

males. One week after the resection of the tumour there were significant reductions in levels of anxiety in both males and females, and the reduction was not affected by hemispheric laterality. Patients with meningioma obtained higher scores of anxiety than groups with other types of brain tumour. However, because the anxiety measurements were performed only during a one week period before and after operation, the finding may reflect acute stress reaction rather than anxiety itself.

In a study performed by Irle *et al*¹⁷ the brain tumour patients (n = 141) with right posterior lesions reported significantly increased levels of anxiety and depression postoperatively compared with patients with right anterior as well as left posterior lesions. Because assessments of the mood state were performed as soon as 2–10 days after resection of the tumour, the authors suggested that the patients' mood changes might reflect the perioperative state rather than distinct changes in the focal brain lesions, and recommended that future studies should analyse changes in mood longer after the operation.¹⁷

To our knowledge, there are no studies so far in which the anxiety of brain tumour patients has been studied by recurrent measurements before and after the operation. Our purpose was to investigate the level of anxiety before the surgical operation of brain tumour as well as three months and one year after the operation; and to evaluate whether the anxiety is associated with tumour laterality. Assessments of gender and tumour histology in anxiety scores are also presented.

Abbreviations: CCEI, Crown-Crisp Experiential Index; CT, computer tomography; FFA, free floating anxiety; HAD, Hospital Anxiety and Depression Scale; MRI, magnetic resonance imaging

Table 1 The items for the free-floating anxiety subscale in CCEI questionnaire²¹

Free-floating anxiety in CCEI questionnaire			
1. Do you often feel upset for no obvious reason?	No = 0	Yes = 2	
2. Have you felt as though you might faint?	Never = 0	Occasionally = 1	Frequently = 2
3. Do you feel uneasy and restless?	Never = 0	Occasionally = 1	Frequently = 2
4. Do you sometimes feel really panicky?	No = 0	Yes = 2	
5. Would you say you were a worrying person?	Not at all = 0	Fairly = 1	Very = 2
6. Do you often feel "strung-up" inside?	No = 0	Yes = 2	
7. Have you ever had the feeling you were "going to pieces"?	No = 0	Yes = 2	
8. Do you have bad dreams which upset you when you wake up?	Never = 0	Sometimes = 1	Frequently = 2

MATERIAL AND METHODS

Patients

The study population consisted of 101 patients aged between 20 and 82 years with a solitary primary brain tumour treated surgically at the Oulu Clinic for Neurosurgery, Oulu University Hospital, between February 1990 and March 1992. Epidemiologically the cohort is a comprehensive and unselected sample of population because the Oulu Clinic for Neurosurgery performs all resections of brain tumours in its catchment area. Geographically this area covers about 49% of Finland. The radiological diagnosis of the brain tumour was carried out by computer tomography (CT) or magnetic resonance imaging (MRI). There were 34 (35%) patients with the tumour located in the right hemisphere and 45 (46%) patients with the tumour located in the left hemisphere. The tumour sited bilaterally in 14 (14%) patients and the location of tumour was undefined in four (4%) cases. Brain CT or MRI was not available in four (4%) patients, excluding them from further study. The database has been documented earlier.¹⁸ Histological grading was done according to the WHO classification.¹⁹ Tumours were divided into following classes: grade I–II gliomas, grade III–IV gliomas, meningiomas, pituitary adenomas, acoustic neurinomas, and other tumours (two hemangiopericytomas, malignant lymphoma, craniopharyngeoma, and two undefined tumours).

We focused our study on supratentorial tumours and our database consisted of 74 patients with a primary brain tumour, 11 males and 15 females with a tumour in the right hemisphere, and 15 males and 20 females with a tumour in the left hemisphere. Of the patients with bilateral tumours, four were males and five females, and all four whose tumours were undefined were females. The database consisted of 30 (41%) male and 44 (59%) female patients. The mean age was 48.2 (SD 12.6) for males and 49.0 (SD 14.0) for females at the time of diagnosing the tumour.

In the group of grade I–II gliomas there were seven patients with tumour in the right hemisphere and 11 with tumour in the left. In grade III–IV gliomas, there were eight right sided and 11 left sided tumours. Eleven of the meningiomas were in the right hemisphere and 13 in the left hemisphere. Of supratentorial tumours nine were located bilaterally.

Anxiety assessment

The level of anxiety was obtained from the Crown-Crisp Experiential Index (CCEI), earlier called the Middlesex Hospital Questionnaire.²¹ According to Crown and Crisp (1974), CCEI has been formulated for three different purposes; to describe normal and deviant groups, to study psychosomatic interrelationships, and as a clinical psychometric test to study the personality change following either psychological or somatic therapies. CCEI has been used in studies on patients with psychiatric²² or somatic diseases^{23, 24} and in studies screening normal population to find neurotic psychopathology.²⁵ CCEI is a self rating scale consisting of six different subscales designed to measure neurotic psychopathology: free-floating anxiety (FFA), phobic anxiety (PHO), obsessiveness (OBS), somatic

Figure 1 The mean anxiety scores according to brain laterality at preoperative, three months, and one year measurements.

anxiety (SOM), depression (DEP), and hysteria (HYS). Each subscale contains eight items and total score in each subscale can vary between 1–16.²¹ The items for free-floating anxiety are seen in table 1.

CCEI has been validated for Finnish population²⁶ and FFA subscale has been found to be a reliable and valid tool for assessing the level of anxiety of patients.²¹

In our study we selected to use only the FFA subscale obtained from CCEI, because anxiety is reported to be the commonest psychiatric symptom in patients with a primary brain tumour.²⁷ The level of anxiety in our study population was measured at three time points: preoperatively as well as three months and one year after resection of the tumour. The patients completed the questionnaire during admission for the surgical operation of a brain tumour, 1–5 days before operation. The questionnaire was administered by a trained psychologist.

Statistical analysis

The subjects were divided into two study groups depending on whether the tumour was situated in the left or right hemisphere of the brain. All statistical analyses were based on non-parametric methods due to non-normal distribution of the main study variable. Comparisons between two independent groups were assessed with Mann-Whitney U test. The differences between repeated measurements of FFA scores were analysed with Wilcoxon signed rank test or Friedman's test. The data was analysed using SPSS version 10.

RESULTS

Figure 1 shows the mean FFA anxiety scores in different measurement points according to the hemisphere of the tumour. Before brain tumour operation mean (SD) anxiety

Table 2 Mean anxiety scores among neurosurgical patients with a primary supratentorial brain tumour according to gender and type of tumour

CCEI anxiety scores*	Tumour in the left hemisphere		Tumour in the right hemisphere	
	n	Mean (SD)	n	Mean (SD)
Gender				
Male patients				
Before operation	11	2.3 (2.2)	7	4.7 (1.6)
Three months after surgery	12	1.9 (1.3)	8	2.2 (1.5)
One year after surgery	10	2.3 (1.6)	5	2.2 (1.3)
Statistical significance, p value†		0.150		0.042
Female patients				
Before operation	16	4.5 (3.4)	9	6.6 (4.1)
Three months after surgery	17	4.1 (2.6)	13	4.1 (2.8)
One year after surgery	17	3.4 (2.6)	11	3.4 (2.1)
Statistical significance, p value†		0.597		0.049
Type of tumour				
Patients with gliomas				
Before operation	16	3.2 (2.4)	10	4.7 (2.0)
Three months after surgery	17	3.1 (2.0)	12	2.4 (1.5)
One year after surgery	15	3.0 (2.2)	7	2.0 (1.2)
Statistical significance, p value†		0.335		0.018
Patients with meningiomas				
Before operation	11	4.2 (4.0)	6	7.5 (4.5)
Three months after surgery	12	3.4 (3.1)	9	4.7 (3.1)
One year after surgery	12	3.0 (2.6)	9	3.9 (2.0)
Statistical significance, p value†		0.441		0.114
Gender and type of tumour				
Male patients with gliomas				
Before operation	8	2.5 (2.6)	7	4.7 (1.6)
Three months after surgery	8	2.3 (0.9)	8	2.3 (1.5)
One year after surgery	6	2.3 (1.9)	5	2.2 (1.3)
Statistical significance, p value†		0.399		0.042
Female patients with gliomas				
Before operation	8	3.9 (2.1)	3	4.7 (3.2)
Three months after surgery	9	3.8 (2.4)	4	2.8 (1.7)
One year after surgery	9	3.4 (2.5)	2	1.5 (0.7)
Statistical significance, p value†		0.739		0.180
Male patients with meningiomas				
Before operation	3	1.7 (0.6)	–	–
Three months after surgery	4	1.3 (1.9)	–	–
One year after surgery	4	2.3 (1.3)	–	–
Statistical significance, p value†		0.102		–
Female patients with meningiomas				
Before operation	8	5.1 (4.4)	6	7.5 (4.5)
Three months after surgery	8	4.5 (3.0)	9	4.7 (3.1)
One year after surgery	8	3.4 (3.0)	9	3.9 (2.0)
Statistical significance, p value†		0.670		0.114

*Non-parametric Wilcoxon signed rank test was used to assess statistical significance for difference in anxiety scores before operation and after the brain surgery.

† Number of cases in different follow up measurements varies due to severe physical condition of some patients before or after the brain surgery.

scores were 3.59 (3.12) among patients with left hemisphere tumour and 5.75 (3.32) among patients with right hemisphere tumour, the difference being statistically significant (Mann-Whitney U test, $Z = -2.14$, $p = 0.032$). The corresponding mean (SD) FFA scores after operation varied from 3.00 (2.34) to 3.38 (2.54). There were no statistically significant differences between the left and right hemispheres in anxiety scores at three months or at one year after the operation.

A statistically significant decline in mean FFA scores from before to after operation was found among patients with right hemisphere tumour (Friedmann test for repeated measures $\chi^2 = 8.40$, $df = 2$, p value = 0.015), the mean (SD) FFA scores being 5.75 (3.32) before operation, 3.38 (2.54) three months after operation and 3.06 (1.91) one year after operation.

A corresponding decline was not observed among patients with left hemisphere tumour. (Friedmann test for repeated

measures $\chi^2 = 3.12$, $df = 2$, p value = 0.210), the mean (SD) FFA scores being 3.59 (3.12) before operation, 3.21 (2.43) three months after operation and 3.00 (2.34) one year after operation.

Table 2 shows the mean anxiety scores at different measurement points according to gender and tumour histology.

The results show that the mean anxiety scores before tumour operation decreased statistically significantly compared to later measurements after operation among male patients ($p = 0.042$), female patients ($p = 0.049$), and those suffering from gliomas ($p = 0.018$) (Wilcoxon signed rank test), if the tumour was situated in the right hemisphere. There was also a decline, although not statistically significant ($p = 0.114$), in the mean anxiety scores from before operation

to three months after operation in the patients with a meningioma in the right hemisphere although not statistically significant ($p = 0.114$) (Wilcoxon signed rank test) and these patients were all females. A corresponding decline in anxiety scores was not found among patients with any tumour in the left hemisphere.

The response rate at each measurements varied from 70.5% to 80%. The results remained the same also when analyses were replicated with the complete data including all the measurements.

DISCUSSION

Anxiety as a mood state has been considered to be one of the most common psychological reactions to any somatic disease.²⁸ Patients' emotional responses to physical illness are inseparably linked to the cognitive-perceptual responses. In the case of primary brain tumour patients, the tumour itself has direct effects on mood state. On the other hand, cognitive and neurological defects caused by the brain tumour affect the patient's mood.²⁹ If anxiety were only a psychological reaction to any serious illness it would be the same regardless of the location of the tumour. However, anxiety and hemispheric laterality in patients with brain lesions has been documented in earlier studies.¹⁻⁴ This suggests there is a biological base of anxiety mimicking psychological anxiety and this biological impact is somehow associated with right hemispheric function.

The major finding of our study was that among patients with a primary supratentorial tumour waiting for operation, those with a tumour in the right hemisphere had substantially higher levels of anxiety compared to those with a tumour located in the left hemisphere. Corresponding differences in the level of anxiety were not found after surgical operation of tumour measured at one year after operation. Our finding is thus in line with the study by Irle and colleagues.¹⁷

In our opinion, there are two theories to explain anxiety lateralisation. The first hypothesis is based on interhemispheric balance. The mood of the whole person reflects that of the dominant hemisphere, which may be dominating for a variety of reasons such as a lesion or anaesthetisation.³⁰ When the right hemisphere is damaged, the left hemisphere is in overactivation state compared with normal equilibrium state, and vice versa. It has been supposed that the right hemisphere is more involved in processing negative emotional information, whereas the left hemisphere specialises in positive emotional information.¹⁻¹³ Lesions in the left hemisphere release the negativity of the right hemisphere, with depression or sadness as a result, while damage to the right hemisphere disinhibits the positivity of the left hemisphere, and secondary mania could follow.¹⁻³⁰ As anxiety is not a positive mood state, we think that this equilibrium theory cannot explain our finding of right lateralisation of anxiety in patients with a primary brain tumour.

The other theory is concerned with transmitter metabolism in the brain. Cummings¹ suggested that psycho-organic syndromes caused by brain damage could be explained by the fact that the two hemispheres have different concentrations of transmitters as well as different behavioural functions, and therefore lateralised lesions in the brain could cause different hemispheric-specific syndromes. Whittle²¹ supports this transmitter theory by suggesting that patients with brain tumours have neuropsychological dysfunction, although the peritumoural brain is structurally intact. This is due to tumour induced neurochemical and metabolic changes in the brain. In rodents with implanted gliomas, measurable [3H]-paroxetine binding uptake sites were found within the tumour, suggesting serotonergic sprouting in peritumoural areas.³² Furthermore, Andersen *et al*³³ found in a study with rats that increased serotonin in the right, but not in the left amygdala is related to anxiety, suggesting that anxiety is associated with right hemispheric function.

The other finding of our study was that in follow up measurements made after three months and after one year of operation, the level of anxiety declined statistically significantly in patients with right hemisphere tumours. A corresponding decline was not observed in patients with tumours in the left hemisphere. According to earlier studies¹⁶⁻¹⁷ and case reports⁸⁻¹¹⁻¹⁵ it has already been shown that if patients with brain tumours had mood symptoms before operation, these symptoms disappeared after the resection of the tumour. Irle called for follow up studies over longer periods after tumour operation.¹⁷ In our study we were able, for the first time, to report anxiety in brain tumour patients by repeated measurements. We found that the level of anxiety remains low until one year after tumour operation, both in patients with the tumour in the right or the left hemisphere. It can thus be suggested that anxiety in patients with a brain tumour did not reflect only the perioperative state. Especially in patients with a right hemisphere tumour, the brain tumour itself caused increased anxiety, which declined after the resection of tumour.

We also observed that our major finding existed in both males and females. In our study the mean FFA scores were generally higher among women compared with men at all measurement points, which parallels epidemiological knowledge that women have two times higher anxiety rates than men. The difference between genders in mean FFA scores has been documented in patients of general practice, mean FFA scores being about 2.8 for males and about twice of that—5.4—for females.²¹ The prevalence of anxiety disorders among the general Finnish population has also been reported to be higher among women (12.3%) than men (5.9%).³⁴ Thus, the difference between genders in our study is due to the difference in prevalence of anxiety between genders rather than the measuring instrument itself.

In preoperative measurements, increased levels of anxiety in patients with right hemisphere tumour were also seen in the subgroups by tumour histology. Thus, our results add some interesting points to the literature. Pringle *et al*¹⁶ found that patients with meningiomas had preoperatively higher levels of anxiety than patients with other types of brain tumours. However, they did not assess the lateralisation effect by the gender on anxiety levels according to different histological subgroups.

The level of anxiety declined immediately after surgery in patients with gliomas in the right hemisphere. A corresponding decrease was not found in patients with gliomas or meningiomas in the left hemisphere. In the patients with a meningioma in the right hemisphere there was also a decline in anxiety scores after surgery of the tumour, but the difference did not reach statistical significance. Interestingly, all these patients were females and this detail might explain the higher scores among these patients at baseline. Our results differ with the study of Irle *et al*,¹⁷ who found that lesions resulting from resection of different neuropathological types of tumours had similar effects on the emotional state of patients. We suggest that gliomas might have more serious effects on brain function—that is, serotonergic dysfunction, than meningiomas.

So far, animal studies have revealed metabolic and neuro-receptor findings of gliomas in the brain.³² However, it is still unknown whether the putative transmitter activity differences in various tumour types also exist in the human brain, and whether tumour histology explains the extent of psychiatric symptomatology in patients.

The limitation of our study might be the small number of patients in the database as a whole, and especially in different subgroups according to histology and laterality. Therefore, our findings are preliminary and have to be taken with caution. Also, some cases were missed during the follow up due to severe dysfunction of the patients' somatic condition—for example, confusion or state of unconsciousness due to raised

intracranial pressure or tumour induced motor aphasia. Unfortunately, the study protocol did not include structured psychiatric diagnostic interviews. The existence of psychiatric symptoms was based on the self-rating scale and—for example, aphasia among patients with a tumour in the left hemisphere may be a bias for information of psychiatric symptoms. However, aphasia was evaluated by a trained psychiatrist at every study point, and language ability in the patients with a tumour in the left or the right hemisphere did not differ significantly from each other in this study. Further, all patients with tumour induced aphasia were in the drop-out group.

In summary, the laterality of anxiety can reflect the differentiation of the two hemispheres. We suggest that a primary supratentorial tumour can cause anxiety symptoms, especially in patients with the tumour located in the right hemisphere of the brain and with gliomas. The level of anxiety declined markedly after surgical resection of the tumour. Further studies are needed to explain the biological mechanisms of anxiety in brain tumour patients. In our opinion, gliomas and the right hemisphere deserve a great deal of histological and anatomical research interest, respectively.

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