CASE REPORT

Considering iatrogenic psychosis after malignant glioma resection

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SUMMARY

It is generally well known that medial temporal lobe resections have been associated with a variety of postoperative neuropsychiatric disturbances. Most of the neurosurgical literature on psychiatric disturbances after a temporal lobectomy concern patients with a strong history of epilepsy; however, relatively few articles have been reported due to a mesial temporal lobectomy following tumour removal. We report the case of a patient who underwent a gross total resection of a malignant astrocytoma in the temporal lobe who developed transient psychosis. Difficulties in diagnosing and predicting this condition are discussed as along with management considerations.

BACKGROUND

Over the past 5 years, the neuro-oncology literature has accepted the benefit of gross total resection (GTR) on survival of patients with malignant gliomas.^{1–5} For tumours in eloquent areas however, GTR may precipitate detrimental effects such as language, motor, sensory or even psychiatric deficits if proper precautions are not taken. Therefore, recently, the idea of a maximal safe resection has been proposed which may maximise the progression free survival (PFS) of patients with malignant tumours. To maximise the safety of these eloquent brain resections, neurosurgeons and neuro-oncologists have utilised a variety of methods such as deep fibre tracking, awake craniotomies, functional MRI and positron emission tomography to map functional areas of the brain to maximise PFS. However, because these methods do not conventionally map mood and personality areas, patients with tumours in certain areas of the brain may be susceptible to a variety of psychiatric disturbances.

It is generally well known that medial temporal lobe resections have been associated with a variety of postoperative neuropsychiatric disturbances.^{6–10} Although this occurrence is rare, it has occurred frequently enough to suggest a pattern and raise further investigation on the topic. Most of the neurosurgical literature on psychiatric disturbances after a temporal lobectomy concern patients with a strong history of epilepsy¹¹; however, relatively few articles have been reported due to a mesial temporal lobectomy following tumour removal.^{7 12} The medial temporal lobe is clinically important in that it is related to declarative memory,¹³ and therefore afflicted in dementias.^{14 15} It is also implicated in epilepsy with a high comorbidity of psychiatric diagnoses such as depression¹⁶ as well as a variety of neuropsychiatric disorders including schizophrenia,

autism and post-traumatic stress disorder.^{17–22} Finally, there is a growing body of literature pointing to the importance of the anteromedial temporal lobe in language from event-related potential,^{23–25} although the association of interictal language impairment has long been known.²⁶

Given its clinical significance we present a case of a patient who unexpectedly suffered from psychosis after a GTR of an infiltrating anaplastic astrocytoma.

CASE PRESENTATION

A middle aged man presented with 6–8 weeks of memory deficits and auditory changes to his primary care physician, who evaluated him for insomnia. After worsening of his cognitive and memory deficits, the patient was hospitalised for 7 days with a presumptive diagnosis of encephalitis. At that time, the patient was examined, and was grossly neurologically intact with no focal signs. During the hospitalisation, MRI revealed a left temporal lobe lesion involving the hippocampus and medial temporal lobe with an observed mass effect on the sylvian fissure and the temporal horn of the left lateral ventricle (figure 1).

Given the proximity of the lesion to Wernicke's area, the patient was scheduled for an awake craniotomy to minimise any potential language deficits.

Figure 1 Preoperative axial T2-weighted MRI showing evidence of expansion and signal hyperintensity in the left temporal lobe, primarily involving the left middle, left superior temporal gyrus, the anteromedial temporal lobe, left insular and subinsular regions and the ipsilateral para-hippocampal area with two areas of nodular enhancement, the more conspicuous measuring 0.95 cm in diameter.

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Figure 2 Postoperative axial T2-weighted MRI describes status post-left frontotemporal craniotomy with large cerebrospinal fluid-filled surgical cavity in the left middle cranial fossa. A small focal nodular area of enhancement is noted in the left temporal lobe posterior to the surgical cavity. No evidence of appearance of contrast enhancement elsewhere in the brain parenchyma.

Under the awake craniotomy protocol, the Wernicke's area was avoided and an anterior left temporal lobectomy was performed with sparing of the insular cortex (figure 2). The pathology was consistent with a grade 3 anaplastic astrocytoma with a Ki-67 index greater than 5%. Based on the pathology, the patient was recommended to undergo chemotherapy and radiation treatment. In the immediate postoperative period, the patient demonstrated mild intermittent aphasia with word finding difficulty, dysnomia and difficulty in following commands. The patient was treated with dexamethasone (10 mg every 6 h), which reduced his aphasia, and returned the patient to his baseline neurological status. At discharge on postoperative day 2, the patient's steroid dosage was reduced from 10 to 6 mg every 6 h. On postoperative day 10, the patient was hospitalised for acute psychosis and agitation thought to be secondary to his corticosteroid therapy and levetiracetam. The psychosis manifested as homicidal and suicidal ideations with bouts of violence and depression. Based on his presentation, the patient was evaluated for oedema-related psychosis or psychiatric disturbances related to the resection.

INVESTIGATIONS

Relevant investigations were conducted in the emergency department after presentation. A complete biochemical and metabolic work-up was conducted which revealed a mild hyponatremia that was present immediately postoperatively. All other metabolites and electrolytes were within normal limits, and the patient was instructed to hold free water intake. At that time, MRI was ordered. With no evidence of oedema on imaging or seizure activity on EEG, the patient's steroid dosage was decreased to 4 mg every 6 h.

DIFFERENTIAL DIAGNOSIS

- Steroid-induced psychosis
- Iatrogenic psychosis secondary to resection of medial temporal lobe
- Delirium secondary to hyponatremia

TREATMENT

Patient's steroid dosage was tapered completely. No psychiatric medications were initiated at this time because the patient left the emergency department against medical advice.

OUTCOME AND FOLLOW-UP

Two weeks after the first psychotic episode, the patient was admitted again to the hospital with suicidal/homicidal ideations with paranoia. At this time, patient's electrolytes were normal, and he was no longer taking steroids. After starting on risperidone, the patient's behaviour changed, stabilised and was discharged from the hospital on day 10. After 15 months of postoperation, the patient has been doing well after completing radiation therapy and chemotherapy, but is still slightly irritable. He reports normal language function and has no further symptoms. He received bevacizumab after completion of standard temozolomide chemotherapy. From a psychiatric standpoint, he currently receives antipsychotics (risperidone) and mood-stabilisers (carbamazepine), which have controlled his psychosis.

DISCUSSION

The incidence of psychiatric complications following temporal lobe resections for tumours has been rarely recognised although it has been adequately characterised in studies of epileptic patients. In the available literature on epileptic patients undergoing temporal lobe surgery, a study by Trimble in 1992 reported a 50% incidence of new onset psychiatric disturbances (anxiety or depression) 6 weeks postoperatively. Additionally, 45% of these patients also reported an increase in emotional instability. Within this study, anxiety and emotional lability decreased while depression worsened 3 months after surgery.¹² In a broader sense, patients with left-sided pathology who underwent temporal lobe surgery also showed an increased risk of mood disorders 1–2 months postoperatively that recovered after 2 years.⁶ Similarly, Siegel *et al*¹⁰ reported a 10% psychiatric morbidity in their study consisting of 75 patients undergoing surgical resection of pathologies predominantly involving the temporal lobe. Another study by Shaw *et al* in 2004 reported a higher percentage of postoperative psychosis, showing that out of 38 patients, nearly one in four developed symptoms of depression. The range of psychiatric morbidity reported even included symptoms of schizophrenia.⁹ However, in these epileptic patients, temporal lobectomies resulted in a cure for the patient in up to 90%. In addition, these postoperative disorders usually remain transient, lasting only from 2 months up to 2 years, while patients remain relatively seizure-free.⁶ For paediatric neurosurgeons, such deficits may be an acceptable cost for these patients. However, for patients with malignant brain tumours with no definitive cure, postoperative psychiatric morbidity may be unwarranted.

The psychosis, which our patient demonstrated, may have been confounded by the administration of dexamethasone and levetiracetam. These drugs are routinely used postsurgically for oedema reduction and seizure prophylaxis. However, both of these drugs have documented neuropsychiatric effects including depression, psychosis, anxiety, mood changes and hallucinations. It is estimated that steroid-induced psychosis may occur in approximately 5% of patients, yet it is unknown how frequent psychosis manifests in terminal illnesses. A study by the Boston Collaborative Drug Surveillance program suggested that during corticosteroid administration, these symptoms may be dose dependent. At doses of prednisone less than 40 mg/day, 1.3% of patients in the study experienced psychiatric side effects

compared with 18.4% at a dose above 80 mg/day. The psychiatric side effects were characterised as clinical depression, psychosis and mania.²⁷ This was confirmed by a large study by Fardet *et al* which showed an increase in suicide and neuropsychiatric disorders in patients taking corticosteroids that appeared to be dose-dependent and also associated with a history of neuropsychiatric symptoms. Older men were also found to be at a higher risk for delirium, confusion, disorientation and mania.²⁸ Notably depression has been associated with levetiracetam administration. Grant²⁹ showed that the prevalence of depression was 1.9% in patients taking 1000 mg/day of levetiracetam, and 5.7% in patients taking 2000 mg/day while compared to 2.7% in those taking a placebo. Psychosis related to levetiracetam use has only been shown in case reports and therefore seems to be a rare complication.³⁰ In our particular case, psychosis was unlikely due to dexamethasone due to the longstanding history of psychosis postoperatively, the continuation of behavioural changes after cessation of steroids, and response to atypical antipsychotics.

For neurosurgical oncologists, recognition of this complication may be crucial to potentially identify risk factors and complications of a temporal lobectomy that have previously been overlooked in brain tumour patients. For example, as neurosurgeons strive to achieve a maximal resection for tumours in the medial temporal lobe, unexpected psychiatric consequences may be a result of this aggressive treatment. However, these consequences must be weighed against the relative gain of an extensive temporal lobectomy. For high-grade malignant tumours, extensive removal may only provide a patient with a few extra months or years compared to a more conservative resection resulting in subtotal resection. The increased survival time has to be juxtaposed against reduced quality of life.

Awake craniotomies aim to reduce operative morbidity by preserving essential language and motor function by intraoperative mapping of functional cortex. In our case, awake craniotomy was used to avoid damage in the receptive language area (Wernicke's area), and maximise the safety of the procedure. However, because awake craniotomies do not conventionally map personality or psyche, our methods were unable to predict the impact of this resection on the patient's psychiatric outcome. In retrospect, an aggressive resection of presumably non-functional tissue may be reconsidered in certain cases of highly malignant tumours. For less malignant tumours, a more aggressive resection with the aim to substantially increase survival may be justified despite the potential psychiatric complications. Nevertheless, our patient's language and psychiatric impairments improved considerably with medication.

Limited studies are available that describe tumour-related temporal lobe resections. It is important that clinicians are aware of

these potential postoperative psychiatric consequences such as psychosis, depression or schizophrenia. Therefore understanding the potential psychiatric consequences, which may arise from a temporal lobectomy, may be of more importance than previously thought. Further investigation of these complications may be warranted to help improve patient quality of life.

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Learning points

- Iatrogenic psychosis after mesial temporal lobe resection is a rare but well-described phenomenon.
- Differentiating between psychosis after medial temporal lobe resection and steroid-induced psychosis is extremely important and may require prompt weaning of steroids.
- Psychiatric complications after such procedures may be permanent and could severely hamper quality of life.
- Antipsychotic medications may be helpful in attenuating symptomatology in the long-term.

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