



## Management of seizure associated with brain tumour

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### How does brain tumour cause seizure?

About 50% of patients with brain tumours are affected by seizure. Partial seizures have the highest incidence, followed by seizures due to secondary generalisation. The type of seizure may vary with different histological subtypes, tumour location and extent. The underlying pathophysiologic mechanisms of tumour-associated seizures are poorly understood and may include alteration of peritumour amino acids, regional metabolism, pH, neuronal or glial enzymes and protein expression, as well as immunologic activity. An involvement of altered distribution and function of N-methyl-d-aspartate (NMDA) subclasses of glutamate receptors also has been suggested<sup>9</sup>. In general, slow-growing benign tumours cause more seizure problem than malignant tumours because rapidly growing malignant tumours tend to destroy nearby neurons instead of stimulating them.

### Oncological management vs. seizure control

When a malignant tumour is suspected, as represented by a rapidly growing tumour with mass effect and peritumoural oedema, the oncological management takes priority. The standard treatment involves surgery aiming at maximal removal of the tumour within safety limits, and followed by radiotherapy and chemotherapy if necessary.

When the tumour is benign looking with an indolent biological behaviour and associated with a long history of chronic seizures, the major concern falls on to seizure control, especially when the seizure is intractable to medications. The majority of these tumours are located at the temporal lobe, which are usually gangliogliomas, pilocytic astrocytomas, or dysembryoplastic neuroepithelial tumours.

### Prescribing antiepileptic drugs (AED) for patients with malignant brain tumours

When prescribing AED in patients with malignant brain tumours, one has to take note of the interaction between AED and the chemotherapeutics. Many AED and chemotherapeutics share common metabolic

pathways via the hepatic cytochrome P450 (CYP) isoenzymes. Phenytoin, carbamazepine, and phenobarbital are potent enzyme-inducing AED (EIAED) that can cause a decrease in the serum concentration of chemotherapeutics, potentially compromising anti-tumour activity. Likewise, chemotherapeutics can alter the pharmacokinetics of EIAED and hence impair seizure control. Other agents, such as valproic acid, are enzyme-inhibiting AED that can impede the metabolism of other drugs, potentially increasing the serum concentrations of chemotherapeutics. Therefore, patients receiving valproic acid with concomitant chemotherapy should be monitored closely. Theoretically, newer generations of AED that are not metabolised by CYP isoenzymes are better options in such situation. Of these, gabapentin and levetiracetam show the most promise.<sup>12</sup>

### How much resection is required to control seizure?

It is important to realize that neurons surrounding the tumour constitute the epileptogenic zone. Removing the tumour alone may not guarantee a good outcome in seizure control. However, it can also be argued that if the irritating lesion is removed, the microenvironment may return to normal and the surrounding neurons may cease to discharge abnormally. There is controversy about the best approach to the problem. Some studies suggest that tumour resection alone is sufficient, while others recommend mapping and resection of the surrounding epileptogenic foci to optimise seizure outcome.

For most surgical series involving paediatric patients, lesionectomy alone yielded very good results.<sup>2, 4, 5</sup> In contrast, studies involving mainly adult patients emphasise the need to map out and remove nearby epileptogenic areas to achieve a satisfactory seizure control.<sup>3, 7, 8</sup>

Chronic seizures, especially those arising from the temporal lobe, are thought to be associated with hippocampal sclerosis through the process of kindling<sup>11</sup>. One of the possible reasons for children to have better results after lesionectomy is that their seizure history is shorter with a lower chance of permanent secondary changes, such as hippocampal sclerosis.

When there is dual pathology, i.e. co-existence of



tumour and hippocampal sclerosis, combined resection of tumour and mesial temporal structure is better than lesionectomy alone. In the study by Lombardi et al, the finding of hippocampal sclerosis on MRI is a predictor of failure of seizure control if only lesionectomy is carried out without hippocampectomy<sup>4,6</sup>.

## How much work-up do we need for surgery?

If the main aim of surgery is for seizure control, one should at least confirm that the relevant EEG abnormalities are related to the tumour by scalp-electrodes recording. A video telemetry with analysis of ictal onset is preferable. However, such recording is usually not precise enough to guide the neurosurgeon for resection of the peritumoural epileptogenic zone, especially if the tumour is situated also at the temporal lobe. Invasive monitoring, such as depth or subdural electrodes recordings, may be required for clear delineation of epileptogenic zone near a tumour. One can perform the recording extra-operatively as a staged procedure before resection or to gather the information at the time of surgery. Before and after removal of the tumour, one may try to look out for the epileptogenic zone by intraoperative electrocorticography (ECoG). However, intra-operative ECoG is not always useful to guide resection of additional non-tumoral tissue<sup>4</sup>. Post-resection spikes on electrocorticography (ECoG) after lesionectomy are common and can be very difficult to interpret<sup>10</sup>.

When there is a plan to resect the hippocampus, a memory function test such as Wada's test may become necessary. Hippocampal resection has been shown to cause material-specific memory impairment with declines in verbal and figural memory after dominant and non-dominant temporal lobectomies, respectively.

If one chooses to take a conservative approach by performing a lesionectomy alone, one can defer all these sophisticated investigations until seizure relapses

after lesionectomy. However, one should prepare the patient psychologically for a possible second operation. Otherwise, it may be misinterpreted as failure of the first surgery and an unnecessary additional operation. Perhaps this staged approach is the only safeguard against unnecessary resection and subsequent harm.

Regardless of the choice of approach, the most important factor in determining good seizure outcome is complete removal of the tumour. Towards this end, sometimes it may be necessary to map out the functional area near a tumour to facilitate total removal and preservation of important functional cortex.

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