Seizure Prophylaxis for Brain Tumour Patients

Brief review and guide for family physicians

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SUMMARY

Brain tumours are relatively uncommon, but family physicians are sometimes confronted with the somewhat unnerving task of carrying on the day-to-day management of these patients. The authors examine some of the problems encountered in preventing seizures among brain tumour patients. Using illustrative clinical cases and a review of the relevant literature, guidelines are provided for the institution, maintenance, and in some cases discontinuation of seizure prophylaxis for this group of patients.

RÉSUMÉ

Les tumeurs cérébrales sont relativement rares, mais il arrive parfois que les médecins de famille soient confrontés à la tâche pénible d'assurer le suivi de ces patients. Les auteurs examinent certaines problèmes entourant la prévention des convulsions chez les patients porteurs d'une tumeur cérébrale. Des illustrations de cas cliniques et une revue de la littérature pertinente ont permis aux auteurs de développer des lignes directrices pour l'institution, le maintien et, dans certains cas, la cessation de la prophylaxie anticonvulsivante dans ce groupe de patients.

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The postoperative or nonoperative care of a patient with a brain tumour is often shared between neurosurgeon, neurologist, and family physician. Seizure prophylaxis for this group of patients is unclear.

Patients with periodic seizures clearly need medication. However, the role of antiepileptic therapy for a patient who has been seizure-free and whose tumour is in remission or has been totally resected is much less clear. Furthermore, long-term antiepileptic medication should be avoided if possible because of the inherent risk of neurologic side effects and systemic toxicity of all such drugs.

We review illustrative case reports of recently encountered cases and the pertinent literature regarding seizure prophylaxis for brain tumour patients. Treatment guidelines are based on tumour type, success of therapy, and seizure history.

Case histories

Case 1. A 45-year-old previously healthy mother of three was referred with a 4-month history of frontal headache. Results of neurologic examination were normal except for bilateral papilledema. Enhanced computed tomography showed a large dural-based lesion in the right frontotemporal region with mass effect (*Figure 1*). Total surgical excision was achieved; the histology was that of a meningioma. Postoperative course was unremarkable, and the patient was discharged home receiving seizure prophylaxis (phenytoin, 300 mg daily), which had been started before surgery.

The patient was reviewed 2 months after surgery, at which time she was free of headaches and papilledema had resolved. She was reviewed again 8 months after surgery and remained well. Computed tomography showed no signs of tumour and also showed complete resolution of the mass effect. Because she remained seizure free, she was given a schedule to wean herself off phenytoin over 3 months.

Five weeks later, she was involved in a single-vehicle accident in which she and her 3-year-old son were killed instantly. There were no other passengers in the car to witness what had happened, but the motorist behind her on the highway reported that her car veered off the road in a gentle curve and struck a pole. The patient's grief-stricken family wondered whether a seizure could have been responsible for her death. They were told that it was possible but unlikely because she had

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Figure 1. **Enhanced CT scan from case 1:** *Homogeneously enhanced left frontal tumour was confirmed as a meningioma at surgery.*

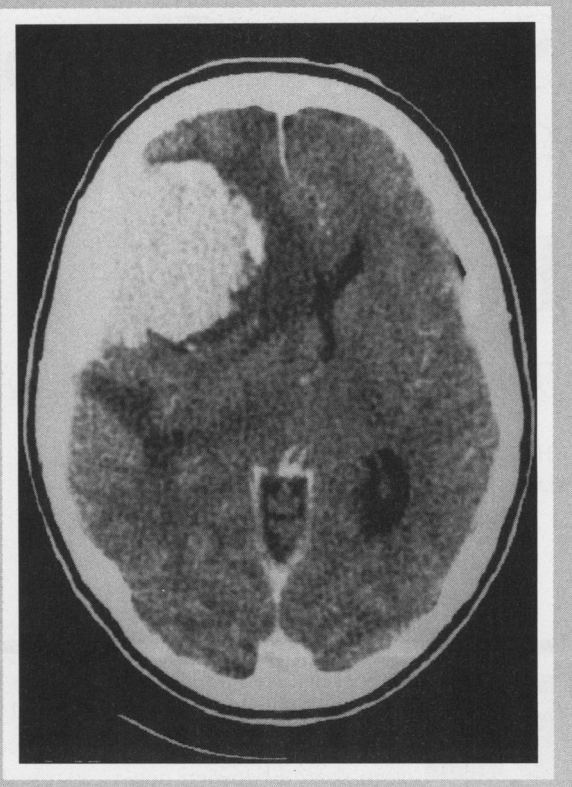


Figure 2. **Computed tomography scan from case 2:** *Low-density lesion in the left occipital lobe has the typical appearance of an infarct and was presumed to be responsible for the right homonymous field loss.*

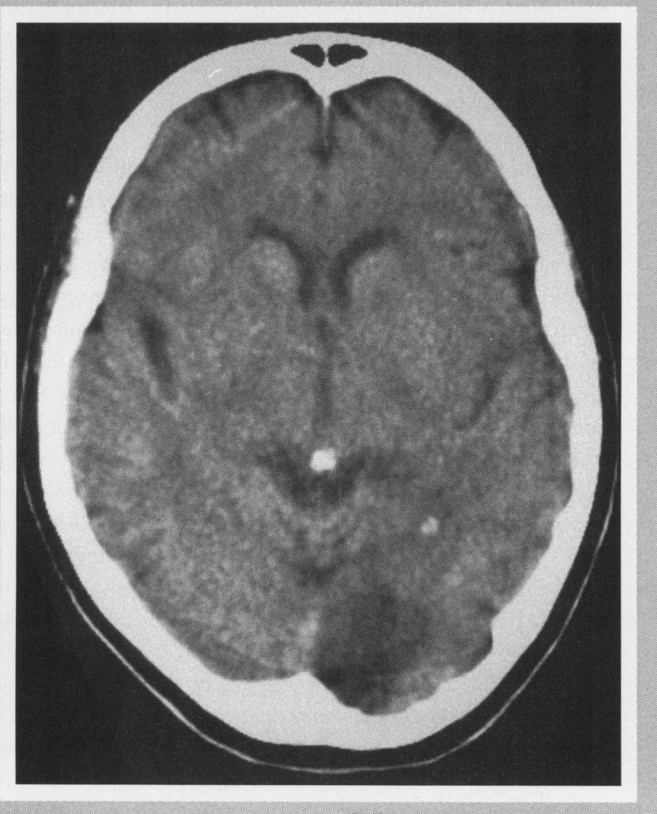


Figure 3. **Higher CT cut from case 2:** *Homogenously enhanced lesion in the left parietal lobe is unrelated to the infarct in the occipital lobe. The lesion is typical of a meningioma.*

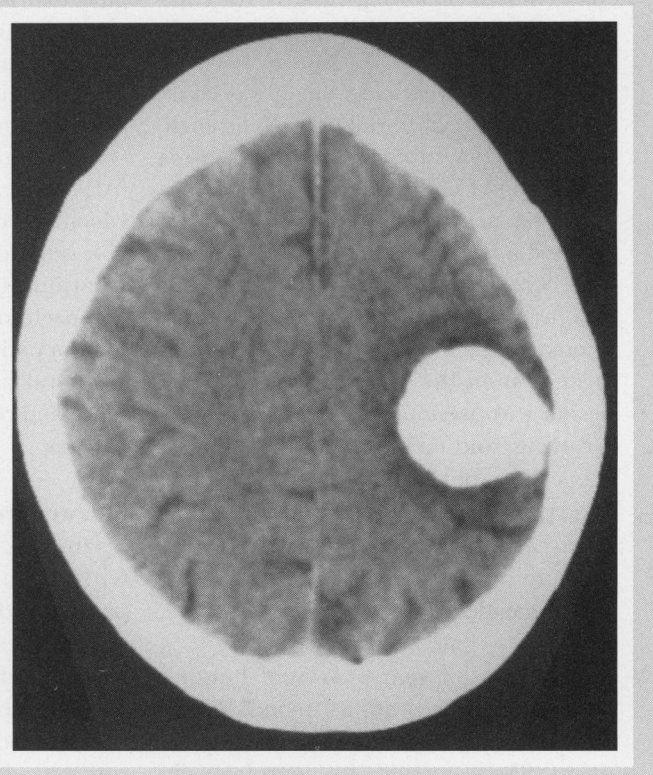
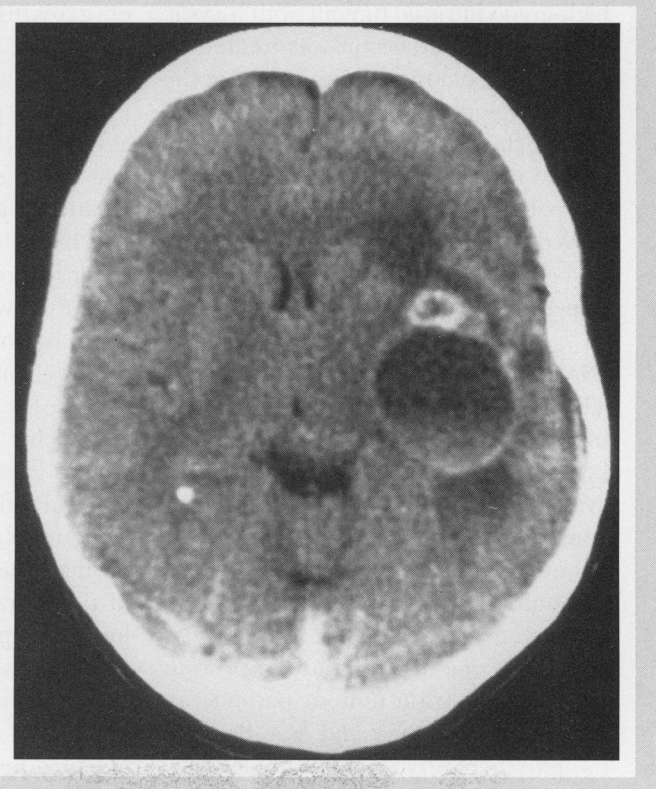


Figure 4. **T1-weighted, coronal slice magnetic resonance image from case 3:** *Left temporal lesion has cystic and solid components. Stereotactic cyst aspiration and tumour biopsy revealed glioblastoma multiforme.*



never had a seizure either before or during the 9 months following curative resection of her benign extra-axial tumour.

Case 2. A 70-year-old woman was investigated for atrial fibrillation. Neurologic examination showed a homonymous hemianopsia in the right field. There was no other neurologic finding. A CT scan showed a left occipital lobe infarct, which was considered responsible for the hemianopsia (*Figure 2*). An incidental meningioma of the left parietal convexity was also seen on the scan (*Figure 3*). As this lesion was presumed to be benign, slow growing, and currently asymptomatic, surgery was not recommended at the time. The patient was followed up with regular clinical and radiologic evaluations. Seizure prophylaxis was, therefore, not recommended.

Case 3. A 63-year-old, right-handed woman presented with a 1-month history of subtle dysphasia and memory impairment. She was otherwise neurologically intact, and a magnetic resonance image (*Figure 4*) showed a lesion in the left temporal lobe with irregular ring enhancement around an area of low density.

The radiologic diagnosis indicated a high-grade intrinsic tumour with a cystic component. The lesion was treated by stereotactic biopsy and aspiration of the cyst. Histology confirmed a glioblastoma multiforme, and she was subsequently treated with cranial radiation. Although this patient had had no seizures, she was started on seizure prophylaxis, which will be continued for the rest of her life (expected to be 1 or 2 years).

Discussion

These cases highlight some of the dilemmas of seizure prophylaxis physicians face in brain tumour patients. Relatively little is available to guide decision making, and consequently family physicians are frequently left to follow up these patients without any scientific basis on which to plan and manage therapy.

On the one hand, failure to prevent seizures in a brain tumour patient can result in severe injury and even death to the patient. Seizures can also severely jeopardize social as well as occupational rehabilitation by making the patient ineligible to drive or to pursue certain occupations. Effective seizure prophylaxis is, therefore, an essential part of the overall management of the seizure-prone patient with a brain tumour.

On the other hand, antiepileptic drugs (AEDs) all carry significant adverse effects, which make their long-term use undesirable beyond what is absolutely necessary. In attempting to formulate a rational approach to seizure prophylaxis for brain tumour patients, physicians should consider several factors that influence the occurrence and control of seizures among these patients.

Seizure frequency

Seizures occur frequently in association with brain tumours.[1-4] Up to 50% of patients with supratentorial tumours have seizures as a presenting symptom.[1,2] The likelihood of seizures is related to the site of the tumour. For instance, seizures are rarely associated with infratentorial tumours. Patients with supratentorial tumours are more likely to have seizures if the tumours are in the motor cortex or the temporal lobe.[1,2] The frequency of seizures is also influenced by tumour type, being more common in the relatively slower growing tumours like oligodendroglioma, meningioma, and low-grade astrocytoma.[1]

Seizures among brain tumour patients also occur as a result of surgical therapy. The risk of epilepsy following craniotomy is variously estimated at 10% to 30%.[1,2,4-8] It is likely that the risk of postoperative epilepsy is related to the site of the operation.[5,6] However, complete removal of a brain tumour can control or even cure seizures. Ramamurthi et al[4] reported cessation of seizures after surgery in 20 of 37 patients (54%) operated on for meningioma. These were all cases in which total removal of the tumour was achieved. Thus a group of patients exists who, despite having seizures as a presenting symptom of their brain tumour, do not require long-term postoperative seizure prophylaxis following complete extirpation of their tumours.

Seizure prophylaxis

Seizure prophylaxis aims to prevent the

occurrence of or, at the very least, reduce the frequency of seizures in patients known to have or suspected to be prone to recurrent seizures. Seizure prophylaxis is, therefore, usually recommended for brain tumour patients in whom seizures have occurred before presentation. However, many brain tumour patients have no history of seizures when they are first seen, and in these patients the decision to recommend seizure prophylaxis is not so clear-cut.

The risk of seizures due to the tumour as well as the risk due to any intracranial surgical procedure, such as might be undertaken to biopsy or excise the tumour, have already been discussed. It is reasonable to assume that these risks are additive and that seizure prophylaxis might be useful in reducing these risks. This was the rationale for commencing seizure prophylaxis in case 1.

On the other hand, the effectiveness of seizure prophylaxis to prevent seizures among patients who have not had seizures is controversial, and some authors have reported no difference in the incidence of seizures among patients given seizure prophylaxis and those not treated.[3,8,10,11] The failure of therapy to prevent seizures in most of these instances could have been attributable to failure to achieve therapeutic serum levels of the drugs, especially in the perioperative period, which several authors identify as a time of especially high risk of seizures.[8-10]

In order to achieve therapeutic levels in the perioperative period, seizure prophylaxis should ideally be started several days before surgery, but as this is often impractical, an intravenous loading dose is usually recommended. It appears that attainment and maintenance of adequate AED levels affords protection against the development of seizures, but further studies are clearly required.[12]

The drugs commonly employed in seizure prophylaxis all have undesirable side effects.[13,14] Phenytoin is the most frequently prescribed drug because of its effectiveness, its availability in a parenteral preparation, and its relatively lower incidence of serious adverse effects. Apart from its gastrointestinal, hematologic, mucocutaneous, hepatotoxic, teratogenic, and various neurologic side effects that are well known,[13] three side effects, though uncommon, are of particular importance for brain tumour patients. First, its interaction with dexamethasone, a drug required by many brain tumour patients, leads to decreased bioavailability of the dexamethasone.[15] Second, some evidence suggests that phenytoin therapy decreases cell-mediated immunity.[16] In brain tumour patients whose immunity is depressed both by their disease and by any adjuvant radiotherapy or chemotherapy that is administered, this side effect is certainly undesirable. Finally, the combination of radiotherapy and phenytoin ingestion has been associated with a few cases of erythema multiforme and Stevens-Johnson syndrome among brain tumour patients.[17]

Similar and other side effects have been noted with the other AEDs. For these reasons, physicians should consider discontinuing seizure prophylaxis for patients who remain seizure free for long periods.

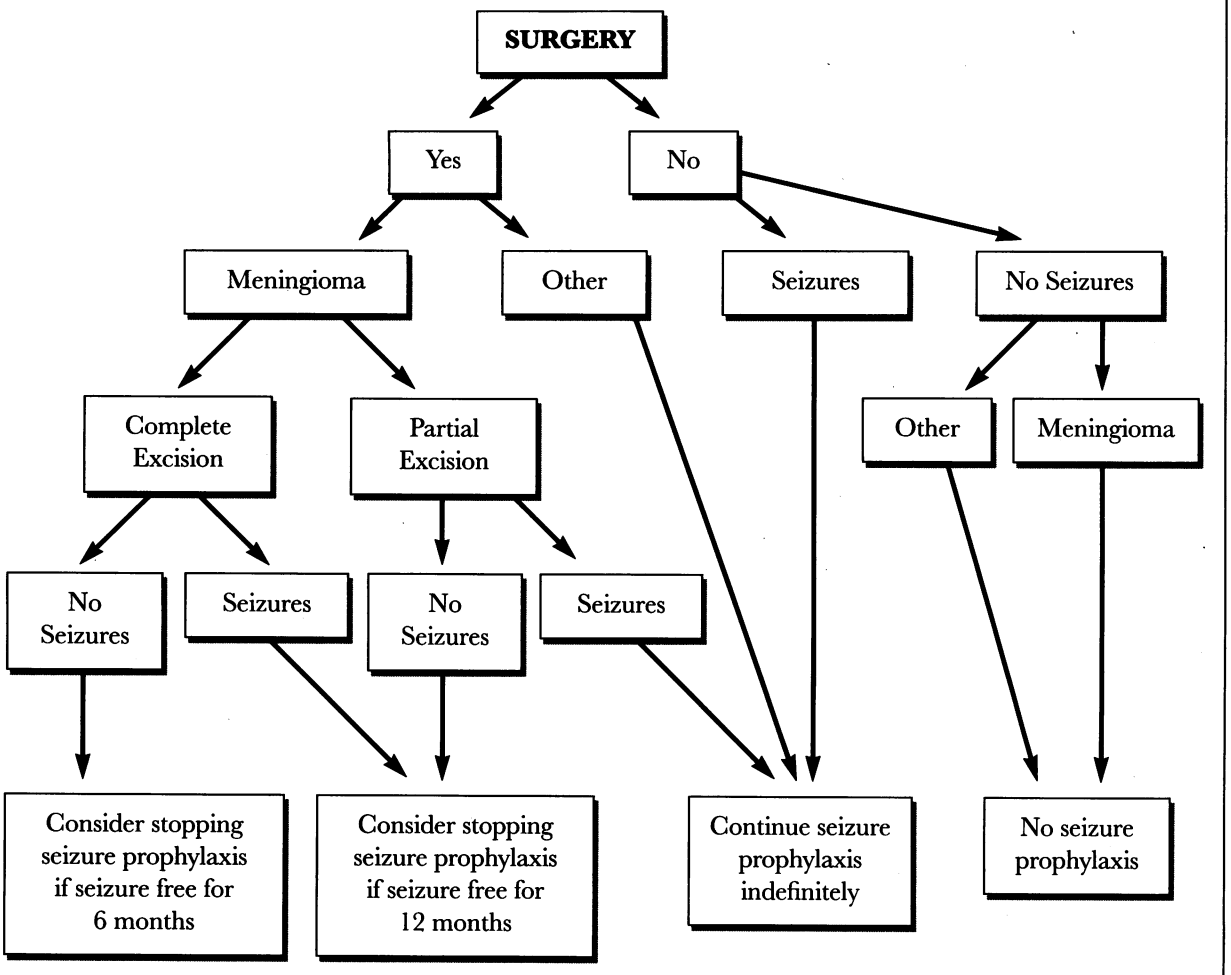
Discontinuing seizure prophylaxis

In considering the discontinuation of seizure prophylaxis in any particular patient, three important questions need to be considered. First, what is the likelihood of relapse among patients whose seizures are well controlled by seizure prophylaxis, and what is the likelihood of de novo seizures in patients who received seizure prophylaxis at the time of surgery but who have had no seizures? Second, what factors help to predict this likelihood? Finally, what is the likely impact of relapse on the individual patient?

For patients who have had at least one seizure, several reports of cessation of AEDs in seizure patients after long seizure-free periods have been published.[18-25] The relapse rate in these series has varied widely from 2% to 60%. No report on the results of discontinuing seizure prophylaxis specifically in brain tumour patients, however, is currently available.

Several factors appear to influence the risk of relapse. The relapse rate was generally lower in the pediatric series than in those including adult patients. Arts et al[20] found a higher relapse rate after discontinuation of seizure prophylaxis among patients with epilepsy from a known cause

Figure 5. **Approach to seizure prophylaxis in supratentorial tumours:** *Infratentorial and pituitary tumours have been excluded and other benign extra-axial tumours (eg, craniopharyngioma) are to be treated as for meningioma.*



(eg, tumours) than among patients with idiopathic epilepsy. Ramamurthi et al[4] found that approximately half of their meningioma patients with seizures before surgery became seizure free after (total) surgical extirpation. Patients who have total surgical excision of a benign tumour will, therefore, theoretically be at less risk of seizure recurrence after seizure prophylaxis is discontinued.

For patients with no previous seizures who begin seizure prophylaxis after surgery, we have little information on the risk of developing seizures after discontinuation of seizure prophylaxis. It is reasonable to assume, however, that this risk is relatively low. It is bound to be lowest when a benign lesion has been completely excised and highest when the tumour is malignant or when only partial excision is possible.

The role of electroencephalography in predicting the relapse rate following discontinuation of AEDs has been examined by several authors.[18,20-25] Callaghan and colleagues[18] found a higher rate of relapse among patients with abnormal EEG results that did not improve during treatment and that remained abnormal at the time of withdrawal of AEDs compared with those whose results from EEGs were normal or became normal during treatment. Although some studies of children have shown the value of abnormal EEG results in predicting relapse after cessation of seizure

prophylaxis,[21,22] adult studies have failed to demonstrate any such correlation.

While it would appear reasonable from these findings that AEDs should be discontinued with great reluctance in patients with severe EEG abnormalities, a normal EEG result does not necessarily imply that relapse will not occur. For this reason, we believe that the decision to withdraw AEDs from any particular patient must be based primarily on the clinical status. Finally, the possible impact on the patient of a relapse after seizure prophylaxis is discontinued must be carefully considered because a relapse could jeopardize the patient's social, economic, and leisure life.

Recommendations

Decisions on whether and when to recommend commencement or discontinuation of seizure prophylaxis must, therefore, be based on several factors, including tumour type, extent of surgical removal, and seizure history. The following recommendations are based on these factors, and are summarized in the accompanying flow diagram (*Figure 5*).

Who should receive prophylaxis? All brain tumour patients presenting with seizure should, of course, receive anticonvulsant agents before surgery and should continue therapy after surgery. In addition, patients with brain tumours who have not had seizures but have had surgery (craniotomy or biopsy) should receive prophylaxis before and after surgery. However, patients with benign brain tumours who are seizure free but in whom surgery is not being performed should not receive seizure prophylaxis unless they subsequently develop a seizure. If the tumour is intrinsic (primary or metastatic), however, we recommend that seizure prophylaxis be started.

How should prophylaxis be administered and monitored? Therapy should begin before surgery if possible, and a loading dose should be administered to ensure adequate levels in the perioperative period of maximum risk. Phenytoin is the first drug of choice in many centres, but carbamazepine, phenobarbital, and valproate sodium are also effective.

Subsequently, therapy should be monitored by checking serum levels monthly or every 2 months for at least the first 6 months. If the patient remains seizure free and free of toxic effects for this period, further frequent measurements of drug levels are probably unwarranted[12] and could be reduced to once a year unless a seizure occurs or toxic effects develop, in which case levels should be measured and dosage adjusted accordingly. Dose changes should be gradual because abrupt changes can cause profound swings in the serum levels.

If toxic effects, multiple seizures, or both occur in the presence of adequate serum levels, consideration should be given to changing the drug or adding another drug. A change of drug should be carried out gradually by simultaneously introducing the new drug in increasing doses while withdrawing the old in decreasing doses. This should be done over at least 1 week.

When should prophylaxis be discontinued? For patients who had preoperative seizures but in whom a benign tumour was completely excised and who remain seizure free for 12 months, it would be reasonable to attempt discontinuation of seizure prophylaxis. Discontinuation of medication should be gradual, over at least 3 months, and patients should be warned of the risk (at least 35%) of relapse following withdrawal of seizure prophylaxis if they have had previous seizures.

The social implications of relapse, especially for driving and occupation, should be discussed fully with the patient before embarking on a trial withdrawal. Patients with total removal of benign tumours who had no seizures either before or after surgery could also be considered for a trial of seizure prophylaxis withdrawal after 6 months of therapy. However, prophylaxis should be continued indefinitely for patients where complete excision is impossible or cases of intrinsic (primary or metastatic) tumours. ■

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