Seizures in palliative care

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Mr J.K. is a 65-year-old man who has stage IV non–small cell lung cancer with recently diagnosed brain metastases. A month ago, he was treated with whole-brain radiotherapy. He takes a low dose of dexamethasone daily (4 mg), from which he is being weaned after irradiation. Today Mr J.K. consults his physician because last night his wife witnessed him have tonic-clonic movements in his left arm, which lasted 3 minutes.

Seizures in the palliative care context can occur in about 13% of cases.[1,2] About 25% to 50% of palliative patients who develop seizure activity have brain metastases.[2,3] Of patients with primary brain tumours, 20% to 45% will present at diagnosis with convulsions[3] and more will develop seizures as their cancer progresses. It is interesting to note that slow-growing primary brain cancers such as oligodendroglioma and low-grade astrocytoma tend to present more often with seizures, with a prevalence of 70% to 100%, unlike the more aggressive glioblastoma, with a prevalence of 10% to 20%.[3,4] It was also noticed that being female could double the risk of developing seizures,[4] and that children with cancer have a higher incidence of seizure activity[2] than adults with cancer do.

Seizures can be caused by structural damage to the brain or by a systemic insult to the brain. Structural damage can be due to primary tumours, metastases, abscesses, reversible posterior leukoencephalopathy syndrome, paraneoplastic limbic encephalitis, hemorrhage, or radiation necrosis. Systemic causes include hypoxia, hypoglycemia, hyperglycemia, hyponatremia (eg, in the syndrome of inappropriate antidiuretic hormone secretion), hypernatremia, low levels of magnesium, hypocalcemia, hypercalcemia, uremia, and hepatic failure, as well as various medications, such as ondansetron, antipsychotics, and chemotherapeutic agents,[1,2] either through their proconvulsant effect or by lowering the seizure threshold.

Table 1. Classification of seizure type

SEIZURE	CHARACTERISTICS	TYPES
Partial or focal seizures	Simple: without loss of consciousness *or* Complex: with loss of consciousness	Motor Sensory Autonomic Affective
Generalized (with loss of consciousness)	Primary or secondary (following partial seizure) With or without aura	Nonconvulsive: • Absence or petit mal Convulsive: • Grand mal or tonic-clonic • Clonic (upper limb, neck, and face contractions) • Myoclonic (limbs) • Tonic (generalized rigidity and falls) • Atonic (sudden loss of muscle tone)

Data from Caraceni et al.[5]

Seizures are classified according to their level of origin in the brain. **Table 1**[5] shows the nomenclature of seizures. An altered state of consciousness can present as a loss of contact with the surroundings or purposeless and automatic behaviour such as snapping fingers, smacking lips, and undressing. Any time a seizure is accompanied by a loss of consciousness, there will follow a postictal state, which might include somnolence, confusion, or a headache, and can last several hours.

History and physical examination

Mr J.K. does not relate any recent changes in his medications except for the decrease in dexamethasone during the past 2 weeks and the addition of hypoglycemic agents 3 weeks ago for the glucose intolerance he developed since taking the steroid. He has had a declining appetite during the past 14 days. He has been having some left-sided paresis, which preceded the diagnosis of the cerebral tumours, but it seems to have worsened since last night. This finding is confirmed on the physical examination.

When a patient develops a seizure, a prompt history and physical examination are useful to determine the cause. A structural cause can be suspected if there was an aura before the seizure, if the seizure was focal, if there were versive eye movements during the seizure, or if the physical examination revealed focal neurologic findings. These latter neurologic findings might disappear within a few hours after the seizure event. A review of the patient's medications should be conducted; for example, determine whether the patient is taking drugs

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that can lower the seizure threshold, experiencing withdrawal from benzodiazepines or alcohol, or weaning from steroids, or has subtherapeutic levels of anticonvulsants. Rarely, a patient might develop severe opioid-induced neurotoxicity accompanied by convulsions. Investigations might be warranted; a complete blood count and a biochemical workup might reveal further potentially reversible anomalies. Cerebrospinal fluid can be cultured for infectious causes and be submitted for cytologic examination.[2] Radiologic investigations such as computed tomographic scan with contrast or preferably magnetic resonance imaging of the brain might reveal a previously unsuspected mass, leptomeningeal disease, progression of brain tumours, or an ischemic or hemorrhagic stroke. Some strokes are secondary to cancer complications or to its treatments (hypercoagulable or hypocoagulable states, tumour cell embolization, occlusion of cerebral arteries, etc).[1,2] An electroencephalogram is warranted if there is the suspicion of subtle seizure activity; however, normal electroencephalogram results will not completely exclude such a diagnosis.[1] Investigations might reveal more than 1 cause of seizures.[1]

Prophylaxis

Anticonvulsant prophylaxis is not recommended in patients with brain tumours, whether primary or metastatic, if the patient has never had any seizures. This is because of the relatively low risk of developing convulsions for most tumours, and the considerable potential burden of antiseizure side effects (drug-drug interactions, sedation, cognitive impairment, etc). However, brain metastases from melanoma, choriocarcinoma, renal cell carcinoma, thyroid papillary cancer, and cancer of the testis might be exceptions, as these cancers might have a higher risk of causing seizures owing to their increased risk of bleeding.[1,5] A small study by Forsyth et al[4] did not show any benefit of seizure prophylaxis, as patients still developed convulsions due to tumour progression or subtherapeutic levels of anticonvulsants on the same order as those patients not taking prophylaxis. Patients should take dexamethasone before, during, and immediately after cerebral radiotherapy to prevent the edema secondary to acute radiation toxicity, which could otherwise provoke seizures.[1]

Treatment

The treatment of seizures will vary according to the frequency of the convulsive episodes, the duration of each episode, and whether there is a reversible cause. Indeed, a first-time seizure with a reversible cause does not require long-term anticonvulsants. On the other hand, a first episode of seizure in a patient with a brain lesion should warrant the institution of long-term anticonvulsants. When this lesion is a known brain tumour (primary or metastatic) and no other reversible cause of seizure activity has been identified, the institution or increase in dosage of a steroid, such as dexamethasone, could be considered as the first-line treatment alongside long-term anticonvulsant treatment.[5,6] If the brain tumour, whether primary or secondary, can be excised surgically, then anticonvulsants might be weaned off after surgery.[5]

If patients require long-term anticonvulsants but are candidates for further chemotherapy, then institution of antiseizure medications with little risk of interaction with the chemotherapeutic agents should be considered. These include levetiracetam, gabapentin, lamotrigine, topiramate, and pregabalin, as they do not induce cytochrome P450 activity.[2] Enzyme-inducing medications to avoid include phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and topiramate.[2]

Table 2[3,5] shows the anticonvulsants usually prescribed for partial and generalized seizures. **Table 3**[3,5] presents the starting doses, therapeutic doses, and side effects of these anticonvulsants. Moribund patients will need to have their usual anticonvulsants changed when the oral route is lost; then the choices are to give medications through sublingual (SL) administration, such as with lorazepam (0.5 to 1 mg every 8 hours); per rectum (PR) with diazepam (10 to 20 mg twice a day), carbamazepine, valproic acid, or phenobarbital (check dosing with a pharmacist)[3,7]; or subcutaneous (SQ) administration with midazolam (30 to 60 mg per 24 hours in a continuous infusion), lorazepam (0.5 to 1 mg every 8 hours), or phenobarbital (200 to 600 mg per 24 hours in a continuous infusion or divided doses).

Table 2. Recommended anticonvulsant according to seizure type

SEIZURE TYPE	FIRST-LINE TREATMENT	SECOND-LINE TREATMENT
Partial (with or without secondary generalized seizure)	Carbamazepine Phenytoin Oxcarbazepine Valproic acid (for secondary generalized seizure)	Phenobarbital Clobazam (for simple partial seizures) Gabapentin Topiramate Lamotrigine Levetiracetam
Generalized		
• Absence	Valproic acid Clonazepam	Clobazam Topiramate Lamotrigine
• Myoclonic	Valproic acid Clonazepam	Clobazam Topiramate
• Tonic-clonic	Carbamazepine Phenytoin Valproic acid	Phenobarbital Oxcarbazepine Topiramate

Data from Beaulieu and Nadeau,[3] and Caraceni et al.[5]

Table 3. Anticonvulsant doses and side effects

ANTICONVULSANT	STARTING DOSE	USUAL EFFECTIVE DOSE	SIDE EFFECTS
Phenytoin	NA	200-500 mg/d in single or divided doses	Drug-drug interactions including dexamethasone, CNS (ataxia), liver, GI, dermatologic, hirsutism, anemia, osteoporosis
Carbamazepine	200 mg/d; increase by 200 mg/wk	300-1600 mg/d in 3-4 divided doses or 2 divided doses if long-acting	Drug-drug interactions, SIADH, CNS (sedation, vertigo, ataxia, diplopia), myelotoxicity
Valproic acid	15 mg/kg daily; 250-500 mg/d, increased weekly by 250 mg/wk	1000-3000 mg/d, up to 60 mg/kg daily (check serum levels) in 3 divided doses or 2 divided doses if long-acting; decrease dose if hepatic failure occurs	Drug-drug interactions, CNS (ataxia, tremors, sedation), weight gain, hair loss, GI, thrombocytopenia, liver toxicity
Oxcarbazepine	300-600 mg/d	900-2400 mg/d; decrease dose if renal failure occurs	Hyponatremia, dizziness, somnolence, nausea, ataxia, diplopia
Phenobarbital	NA	60-250 mg/d, maximum 600 mg/d (1-5 mg/kg in adults) in single or divided doses; decrease dose if renal or hepatic failure occur	Drug-drug interactions, CNS depressor, respiratory depression, somnolence, rash
Gabapentin	NA	300-3600 mg/d as monotherapy; up to 1800 mg/d as adjuvant therapy, in 3-4 divided doses; decrease dose if renal failure occurs	Interaction with antacids; decrease in memory and concentration; somnolence, ataxia, dizziness, edema, weight gain
Lamotrigine	50 mg/d for 2 wk, then increase by 25-50 mg/wk	100-500 mg/d in 2 divided doses; decrease dose if renal or hepatic failure occur	Rash, especially if dose escalation is rapid
Topiramate	25 mg/d; increase by 25-50 mg/wk	75-400 mg/d in 2 divided doses; decrease dose if renal failure occurs	Drug-drug interactions, somnolence, confusion, weight loss, metabolic acidosis, angle-closure glaucoma
Levetiracetam	750-1000 mg/d	1000-3000 mg/d in 2 divided doses; decrease dose if renal failure occurs	Anxiety, aggressivity, somnolence, asthenia, dizziness
Clobazam	10 mg/d	10-30 mg/d, maximum 60-80 mg/d in 2 divided doses	Same as for benzodiazepines; rash
Clonazepam	NA	1-6 mg/d in 2-3 divided doses	Same as for benzodiazepines; paradoxical excitation

CNS—central nervous system, GI—gastrointestinal, NA—not applicable, SIADH—syndrome of inappropriate antidiuretic hormone secretion.
Data from Beaulieu and Nadeau,[3] and Caraceni et al.[5]

Status epilepticus

Status epilepticus has traditionally been defined as either seizure activity, convulsive or nonconvulsive, lasting longer than 30 minutes, or 3 episodes without return of consciousness within a 30-minute span.[5,6] It carries a mortality risk of 11% to 34%,[3] with acidosis, rhabdomyolysis, and cerebral damage as further complications. With a prolonged convulsive episode, neuronal injury will make pharmacoresistance more likely and anticonvulsants less effective.[5,8] Because the probability of spontaneous resolution of the seizure decreases with time, treatment of status epilepticus should be instituted when a convulsion lasts 5 minutes or more. The treatment might vary according to the patient's location: home care, hospice, or hospital.

In hospital, intravenous (IV) access, blood pressure monitoring, and electrocardiogram can be the routine of the initial handling of status epilepticus. Patients should be positioned in such a way that they cannot hurt themselves; airways should be maintained; and supplemental oxygen should be provided as necessary. In a palliative care population, it is not always possible to obtain venous access and medications will be given by an alternate route, mostly by SQ, SL, intranasal, or PR administration. It is also not always indicated to have such aggressive monitoring, which might be the case on a palliative care unit or in home care.

In all settings, lorazepam is the drug of choice,[7,9] for its speed of activity (3 minutes via IV administration[5]), duration of effectiveness (8 to 24 hours[5]), and ease of administration. Dosage recommendations vary, but a 2-mg dose can be given by IV, SQ, SL, or PR administration,[7] and repeated 10 minutes later if the seizure continues. Alternatively, administer 10 mg of

diazepam PR or by IV and repeat every 5 minutes until it is effective—a maximum total dose of 40 mg[3,7] could be used. Midazolam is also a very good alternative, 5 to 10 mg[3,7] either IV or SQ, and possibly by buccal or intranasal (0.2 mg/kg)[3] administration as some research seems to show.[9] Midazolam could be repeated every 15 minutes up to a total of 3 times.[3] At this step, some would suggest the simultaneous initiation of IV phenytoin.[3] Others would recommend phenytoin only if there is no response to the benzodiazepine.[5-7] The phenytoin dose is 15 to 20 mg/kg every 24 hours, at a rate not exceeding 50 mg per minute.[5-7] Another choice of anticonvulsant at this third step could be phenobarbital. Phenobarbital carries a risk of respiratory failure, especially after the use of benzodiazepines.[5,6] The phenobarbital dose is 10 to 15 mg/kg infused at a rate of 100 mg per minute,[7] for a maximum total dose of 1 g. Alternatively, 20 mg/kg of phenobarbital infused at a rate of 60 mg per minute has also been recommended.[5] Phenobarbital can also be given by SQ administration,[3] which makes it easier to use in a hospice or home-care setting. If the seizure is refractory, persisting despite the use of 2 or 3 different anticonvulsants, the recommendation is intubation and transfer to the intensive care unit for treatment with propofol or pentobarbital,[3,5,7,8] should the patient's prognosis and goals of care allow for aggressive treatment.

A differential diagnosis of status epilepticus should include syncope, transient ischemic attacks, arrhythmia, Munchausen syndrome, and other psychiatric disturbances, parasomnias, and deliriums.[5] Another complicating factor for diagnosing status epilepticus is the existence of *nonconvulsive* partial complex status epilepticus. These seizures are more often secondary to metabolic disorders, presenting as confusion that might be continuous or recurring, with partial complex seizures and recovery of consciousness between episodes—the entire status lasting 1 to 10 days. Nonconvulsive partial complex status epilepticus might resemble delirium with automatisms or psychotic behaviour or affective changes. Unlike convulsive status epilepticus, it does not lead to cerebral damage and therefore its treatment can be more progressive.[5]

Conclusion

Mr J.K.'s management involves increasing his dexamethasone dose, the addition of 100 mg of phenytoin 3 times daily, as well as doing bloodwork. The results of Mr J.K.'s bloodwork do not reveal any biochemical anomalies. A repeat computed tomographic scan of the brain shows increased edema and stable size of the metastases. He has no convulsions for the following 2 months.

Mr J.K. develops progressive generalized weakness and is admitted to a hospice. One evening, he has a generalized tonic-clonic seizure, which lasts longer than 5 minutes. The nurse uses the convulsion protocol written by the admitting doctor: 10 mg of midazolam SQ and 1 mg of lorazepam SL, which are administered simultaneously within 10 minutes of the beginning of the seizure. Five minutes later, there is a decrease in the amplitude of the clonic movements, and within another 5 minutes the clonic movements cease altogether. Unfortunately, Mr J.K. never regains consciousness and dies the next morning, peacefully, with his family by his bedside.

The presence of seizures can be traumatizing for the patient and the family. Seizures might signal the progression of underlying brain lesions; however, there might be other reversible causes.[10] Proper management must include reassurance and education of the patient and family, as well as prescriptions for the acute management of future episodes of seizures whether care is in the home or a palliative care unit. Most seizures can be controlled with prompt treatment with

BOTTOM LINE

- Seizures might signal the progression of underlying brain lesions or, alternatively, be due to biochemical or drug imbalances. When a patient develops a seizure, a prompt history and physical examination are useful to determine the cause.
- The presence of seizures can be traumatizing for patients and their families. Proper management must include reassurance and education of patients and families, as well as prescriptions for the acute management of future episodes of seizures.
- Because the probability of spontaneous resolution of the seizure decreases with time, treatment of status epilepticus should be instituted when a convulsion lasts 5 minutes or more. Treatment might vary according to the patient's location of care.
- Most seizures can be controlled with prompt treatment with benzodiazepines, and although status epilepticus might be a terminal event, it can be made to be as peaceful as possible.

Palliative Care Files is a quarterly series in *Canadian Family Physician* written by members of the Palliative Care Committee of the College of Family Physicians of Canada. The series explores common situations experienced by family physicians doing palliative care as part of their primary care practice. Please send any ideas for future articles to **palliative_care@cfpc.ca.**

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Competing interests

Dr Tradounsky is a member of a continuing education committee that is organizing a conference at McGill University, for which both Purdue and Paladin have given small, unrestricted grants.

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