Seizures and Epilepsy Management in Palliative Care

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Diagnosis of Epilepsy

EPILEPSY

CAUSES OF SEIZURES IN CANCER

DIAGNOSIS AND INVESTIGATION

TREATMENT OPTIONS

STATUS EPILEPTICUS
Epilepsy and Cancer

• The overall incidence of epilepsy in developed countries is about 50/100 000 persons/year
• Cumulative lifetime incidence of seizures is over 10%
• Cancer affects one in three people overall
• Cancer may influence the incidence, treatment and prognosis of seizures and epilepsy
Causes of Epilepsy

• Depends on age and geographical location

• Idiopathic 83% if <9 yrs
• Vascular disease 49% if >60 yrs

• Tumour 6% overall
  • <30 yrs 1%
  • 50-59 yrs 19%
  • >60 yrs 11%
  (35% primary, 59% metastases, 6% unknown)
Causes of Seizures and Epilepsy

• Seizures found to occur in 13% of all patients with cancer
  • Half attributed to intracranial metastases and remainder to metabolic disturbances

• A considerable proportion of seizures among adults with systemic cancer arises due to intracranial metastases
Causes of Seizures and Epilepsy

- Low grade tumours are the most epileptogenic

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Seizure Incidence</th>
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<tbody>
<tr>
<td>DNET</td>
<td>Up to 100%</td>
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<tr>
<td>Oligodendroglioma*</td>
<td>89%–90%</td>
</tr>
<tr>
<td>Ganglioglioma*</td>
<td>80%–90%</td>
</tr>
<tr>
<td>Astrocytoma*</td>
<td>60%–75%</td>
</tr>
<tr>
<td>Meningioma</td>
<td>29%–60%</td>
</tr>
<tr>
<td>Glioblastoma multiforme**</td>
<td>29%–40%</td>
</tr>
<tr>
<td>Metastases</td>
<td>20%–35%</td>
</tr>
<tr>
<td>Leptomeningeal tumor</td>
<td>10%–15%</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>10%</td>
</tr>
</tbody>
</table>

Dysembryoplastic neuroepithelial tumour
Causes of Seizures and Epilepsy

• Seizures that occur in patients with cancer may have a variety of causes
  • Brain parenchymal and meningeal metastases
  • Administration of cytotoxic chemotherapy
  • Toxic–metabolic encephalopathy
Intracranial Metastases

• Brain metastases are less likely than primary brain tumours to cause seizures
  • Headaches, changes in behaviour and mental status are more common manifestations
  • Intracranial metastases often involve the posterior fossa

• Lung cancer (both non-small cell and small cell) is the most common cancer associated with metastases presenting with seizures
  • Breast
  • Malignant melanoma
  • Colon
Intracranial Metastases

• The time interval between diagnosis of the primary tumour and occurrence of seizures due to metastases depends on the propensity of the primary tumour to metastasise to the brain

• Central nervous system metastases can occur early or on presentation for lung cancers and malignant melanoma
  • However these may be delayed by as much as 2–3 years in breast cancers

• Seizures are usually a manifestation of parenchymal metastases but may also be a feature of leptomeningeal metastases
Drug Induced Seizures

• In patients receiving chemotherapy for cancer the possibility of drug-induced seizures should be considered

• Criteria for diagnosis of drug induced seizures include
  • Development of encephalopathy and seizures during or shortly after administration of the drug
  • Exclusion of other metabolic and structural factors and
  • Exclusion of seizures produced by concomitant drugs

• Most drug-induced seizures occur within hours or days of cancer drug administration

• Can occur after several days if the half life of the drug is prolonged as a result of impaired hepatic or renal clearance
Drug Induced Seizures

• Drugs which can cause seizures include
  • Cisplatin – seizures reported in toxicity, PRES
  • Busulphan – seizures and encephalopathy
  • Chlorambucil – seizures in accidental overdoses
  • 5-Fluorouracil – encephalopathy and seizures reported
  • Interferon alpha – seizures in 1-4% reported
  • Cyclosporin – associated with PRES
Reversible Posterior Encephalopathy Syndrome (PRES)

• Drugs
• Metabolic
• Uncontrolled hypertension

• Presentation
  • Headache
  • Seizures
  • Altered mental state and cortical visual loss
    • [an encephalitis presentation with normal CSF]

• Treatment of the inciting factor and control of seizures
Neurological Paraneoplastic Syndromes

• Limbic encephalitis
  • Characterised by focal seizures or status epilepticus with cognitive impairment
  • Seizures can be among the presenting manifestations or occur later during the course of the illness in 50% of cases
  • Rarely seizures may be the predominant manifestation
  • The symptoms may precede detection of the cancer by up to 3 years
Neurological Paraneoplastic Syndromes

- Imaging may show high-signal areas in the anteromesial temporal lobes and/or the basal frontal lobes

- Antibodies - Anti-Hu (SCLC), Ma2 (testicular), CV2/CRMP5 (SCLC/thymoma), ampiphysin (Breast/SCLC), AMPAR (SLCL, breast, ovarian)

- Focal status epilepticus (Epilepsia partialis continua)
  - Focal lesions, involving the frontal motor cortex
  - Histopathological examination shows focal or multifocal perivascular lymphocytic infiltrates in the cortex and brain stem
Paraneoplastic limbic encephalitis
Cerebrovascular Complications

Venous Sinus Thrombosis

- Can present with seizures especially when occlusion leads to the development of cerebral parenchymal infarcts or haemorrhages
- May occur because of occlusion of the venous sinuses by leukaemic infiltrates
- Invasion of sinuses from dural metastases, solid tumours or administration of cancer drugs
Cerebrovascular Complications

Intracerebral haemorrhage

• Parenchymal brain haemorrhages
  • Seizures
  • Headaches
  • Focal neurological deficits

• Acute myeloid leukaemia (coagulation defects predispose to haemorrhage)

• Malignant melanoma and choriocarcinoma are associated with haemorrhagic cerebral metastases
CNS Infections

- Seizures can be the manifestation of infectious processes involving the parenchymal cortex
- Viral infections can involve the limbic and neocortex
  - Herpes simplex
  - Human herpes virus 6 and 7
  - Focal mass lesions due to aspergillosis, nocardiosis and toxoplasmosis
- Meningitic infections, cryptococcal meningitis and subcortical disorders such as progressive multifocal leucoencephalopathy are less likely to cause seizures
Cranial Irradiation

- Seizures may be among the presenting features of both acute radiation encephalopathy and delayed radiation necrosis.
- Rarely they may be the dominant manifestation, and in such cases likely to be refractory to medical treatment.
- Cranial irradiation may also lead to the development of cavernous haemangioma.
  - Typically associated with intractable epilepsy due to repeated minor haemorrhages.
Seizure vs Epilepsy

• A seizure is an episode of neuronal hyperexcitability causing neurological symptoms

• Epilepsy is recurrent unprovoked episodes of seizures
Classification of Epileptic Seizures

- Seizure
  - Focal Epilepsy
    - Focal
    - Focal/loss of awareness
    - Secondary generalised tonic-clonic seizure
  - Generalised Epilepsy
    - Absence
      - Tonic-clonic
    - Generalised tonic-clonic seizures
Focal Epilepsy

• Symptoms depend on the part of the brain where the seizure originates, but also the area that it spreads to
  • Temporal aura – taste, smell, deja-vu
  • Occipital seizures – visual aura

• Focal seizure
• Focal seizure with impaired awareness
• Secondary generalised tonic-clonic seizures
  • May occur with or without warning
Diagnosis

- Epilepsy is a clinical diagnosis
- Most important – accurate history / eye-witness account
- MRI brain imaging required in adults with new onset seizures
- EEG can aid classification of seizure type
Investigations of seizures in patients with cancer
Investigations

• MRI +/- GAD
• Lumbar puncture
  • Cell count, glucose paired with serum, protein, MC&S and viral PCR
• Onconeural antibodies
Treatment of Epilepsy

• When to start treatment?

• First-line AED?

• Which AEDs?
Treatment

- Antiepileptic drugs (AEDs)
  - Hampered by side effects
  - Interactions with other drugs or anti-cancer agents
  - More than 30% of patients will be refractory to AED treatment during the course of their disease despite AED treatment

- Tumour-directed treatment

- Surgical management
MESS study (Multicentre study of Early epilepsy and Single Seizures)

- Children and adults in whom the clinician felt uncertain as to whether AEDs were appropriate
- Randomised to immediate or deferred treatment
- Approximately 1400 patients followed up for >5 years
- For people with single seizures and early epilepsy
  - Early AED treatment has no effect upon long term prognosis or QOL
  - Treatment decisions should based largely upon risk of recurrence
Seizure recurrence depending on risk group

• No benefit of early treatment for those at low risk
  • (patients with a single seizure and normal EEG, no neurological deficit)

• Those with multiple seizures +/- abnormal EEG +/- neurological deficit or abnormal imaging may benefit from early AED treatment
Treatments for Epilepsy

Up to 1990

• Barbiturates
• Phenytoin
• Carbamazepine
• Valproate
• Benzodiazepines

By 2019

• Vigabatrin
• Lamotrigine
• Gabapentin
• Topiramate
• Tiagabine
• Oxcarbazepine
• Levetiracetam
• Pregabalin
• Zonisamide
• Lacosamide
• Brivaracetam
• Perampanel
• Rufinamide
• Sulthiame
Principles of Treatment

• Monotherapy
• Cautious dosage escalation
• Titrate to maximally tolerated dose
• Alternative monotherapy
• Dual-therapy
First line Anti-epileptic Drug

• Traditional treatment choice (pre-2000)

• Focal epilepsy
  • CBZ
  • VPA less effective
SANAD (Standard And New Antiepileptic Drugs)

• Inclusion criteria
  • Aged 5 or over
  • Two or more unprovoked seizures
  • Required treatment with antiepileptic drug monotherapy
SANAD – Arm A
Focal epilepsy A

Carbamazepine is first line AED
SANAD – Focal epilepsy

• Lamotrigine is significantly less likely to fail than Carbamazepine, Gabapentin, or Topiramate
• Lamotrigine efficacy is similar to Carbamazepine but better tolerated
• Lamotrigine should be considered the first line AED for patients with focal onset seizures

• Lamotrigine
  • Slow titration
  • Allergic reaction (can be severe Steven-Johnsons)
  • Insomnia
Anti-epileptic drug options

- Levetiracetam
  - Rapid titration
  - Mood disturbance 1/10

- Time to first seizure 6 and 26 weeks
- Similar for Lamotrigine and Levetiracetam in spite of quicker titration with Levetiracetam
Newer AEDs - Advantages

- Efficacy similar
- Tolerability
  - Lamotrigine v Carbamazepine, Levetiracetam v Carbamazepine
- Long term tolerability
  - Phenytoin – cosmetic, gum hypertrophy, neuropathy, ataxia
  - Phenytoin, Carbamazepine, Valproate - osteoporosis
- Drug interactions
  - Older AEDs enzyme inducers (Phenytoin, Carbamazepine) or inhibitors (Valproate)
  - Multiple interactions with commonly used drugs (eg warfarin, OCP, digoxin, statins)
  - Newer AEDs no or very few interactions
Failed Monotherapy

Failed monotherapy

- Switch to second drug
  - Less overall AED burden
  - Less side effects
  - Cost
  - Compliance

- Add on second drug
  - More effective seizure control
  - More side effects
  - Teratogenesis
Add-on AED

• Co-morbidities important

• Rational polypharmacy

• Individualised treatment
  • Obesity (Valproate v Topiramate)
  • Depression / anxiety (Topiramate / Levetiracetam / Zonisamide v older AEDs)
  • Migraine (Topiramate)
  • Other medical conditions (newer v older AEDs)
Status Epilepticus

- Most common cause is non-compliance with medications in known epileptics
- 25% of status epilepticus cases are non-epileptic
- Critical that decisions are made in a timely manner
- Delays increase the likelihood of refractory and super-refractory status epilepticus
- Consider other causes drugs inc. alcohol, metabolic, infection, encephalitis
- Always check blood glucose
Status Epilepticus: Management

Give the usual AEDs...

- The following AEDs have liquid or dispersible formulations
  - Carbamazepine (can also be given rectally – see BNF for guidance)
  - Clobazam
  - Lacosamide
  - Lamotrigine
  - Levetiracetam
  - Phenobarbitone
  - Phenytoin
  - Primidone
  - Topiramate (sprinkle capsules – the internal powder can be dissolved in water)
  - Valproate*
  - Zonisamide (capsules – the internal powder can be dissolved in water)
Status Epilepticus: Management
Give the usual AEDs...

• The following AEDs can be given intravenously if there is no oral route
  • Phenytoin
  • Valproate
  • Levetiracetam
  • Lacosamide
  • Phenobarbitone
# Status Epilepticus: Management

<table>
<thead>
<tr>
<th>Early Status Epilepticus</th>
<th>Treatment</th>
</tr>
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</table>
| **1st stage (0–10 minutes)** | **Lorazepam (intravenous) 0.1 mg/kg (usually a 4 mg bolus,**  
| • Secure airway and resuscitate | • Repeated once after 10–20 minutes  
| • Administer oxygen |  
| • Assess cardiorespiratory function |  
| • Establish intravenous access |  |
## Early Status Epilepticus

<table>
<thead>
<tr>
<th>Early Status Epilepticus</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd stage (0–30 minutes)</td>
<td></td>
</tr>
<tr>
<td>• Institute regular monitoring</td>
<td>• Give usual AED medication if already on treatment</td>
</tr>
<tr>
<td>• Consider the possibility of non-epileptic status</td>
<td>• Administer glucose (50 ml of 50% solution) and/or intravenous thiamine (250 mg) as high potency intravenous</td>
</tr>
<tr>
<td>• Emergency AED therapy</td>
<td>• Pabrinex if any suggestion of alcohol abuse or impaired nutrition</td>
</tr>
<tr>
<td>• Emergency investigations</td>
<td>• Treat acidosis if severe</td>
</tr>
</tbody>
</table>
### Status Epilepticus: Management

<table>
<thead>
<tr>
<th>Established Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3rd stage (0–60 minutes)</strong></td>
<td><strong>Phenytoin infusion at a dose of 20 mg/kg at a rate of 50 mg/minute</strong></td>
</tr>
<tr>
<td>- Establish aetiology</td>
<td>- Or fosphenytoin infusion at a dose of 15–20 mg phenytoin equivalents (PE)/kg at a rate of 50–100 mg PE/minute</td>
</tr>
<tr>
<td>- ITU</td>
<td>- Or phenobarbital bolus of 10–15 mg/kg at a rate of 100 mg/minute</td>
</tr>
<tr>
<td>- Pressor therapy when appropriate</td>
<td><strong>Pressor therapy when appropriate</strong></td>
</tr>
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<tr>
<td><strong>3rd stage (0–60 minutes)</strong></td>
<td>• Or levetiracetam 30mg/kg (max 3000 mg)</td>
</tr>
<tr>
<td>• Establish aetiology</td>
<td>• Or sodium valproate 30mg/kg (max 3000 mg)</td>
</tr>
<tr>
<td>• ITU</td>
<td>• Contraindicated in women of childbearing age</td>
</tr>
<tr>
<td>• Pressor therapy when appropriate</td>
<td>• Severe liver failure or mitochondrial disorder</td>
</tr>
</tbody>
</table>
Status Epilepticus: Management

- Levetiracetam vs phenytoin in the management of status epilepticus
- Prospective randomised study
- IV levetiracetam had comparable efficacy to phenytoin at achieving seizure control
- Valproate, non inferiority to phenytoin
<table>
<thead>
<tr>
<th>Refractory status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th stage (30–90 minutes)</td>
<td><strong>GA:</strong></td>
</tr>
<tr>
<td>• Transfer to intensive care</td>
<td>• Thiopental sodium (3–5 mg/kg bolus, then 3–5 mg/kg/hour) titrated to effect; after 2–3 days infusion rate needs reduction as fat stores are saturated</td>
</tr>
<tr>
<td>• Establish intensive care and EEG monitoring</td>
<td>• Midazolam (0.1–0.2 mg/kg bolus, then 0.05–0.5 mg/kg/hour) titrated to effect</td>
</tr>
<tr>
<td>• Initiate intracranial pressure monitoring where appropriate</td>
<td>• Propofol (1–2 mg/kg bolus, then 2–10 mg/kg/hour) titrated to effect</td>
</tr>
<tr>
<td>• Initiate long-term, maintenance AED therapy</td>
<td>• Anaesthetic continued for 12–24 hours after the last clinical or electrographic seizure, then dose tapered</td>
</tr>
</tbody>
</table>
Questions?