Chapter 8: Neuropsychiatric aspects of epilepsy

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1 Introduction

Definition – A seizure is a “transient occurrence of symptoms and/or signs due to abnormal excessive or synchronous neuronal activity in the brain” (Fischer et al., 2014). Epilepsy involves two or more unprovoked seizures, or the diagnosis of an epilepsy syndrome.

The classification of epilepsies according to the International League Against Epilepsy (ILAE) was updated in 2017. The classification approach is now an operational/practical classification. The classification system has three levels: Seizure type (Figure 1), Epilepsy type and Epilepsy syndrome. Changes to the diagnostic classification include:

- The term ‘complex’ as in ‘complex partial’ has been removed from the new classification and is replaced by ‘focal impaired awareness’. Whereas ‘simple partial’ is now defined as ‘focal aware’.
- Aura has been removed in the new classification; it is now considered part of the seizure as there are associated changes on EEG.
- The term convulsion has been removed as well, as it implies a motor component.
- Aware versus impaired awareness added, and loss of consciousness has been removed.
- A separate subtype is focal to bilateral tonic-clonic seizures, which replaces the prior term ‘secondarily generalized tonic-clonic’.

Seizures are first classified according to their onset (Figure 2). Clinicians should also attempt to identify the aetiology of the patient’s epilepsy (Figure 3).
ILAE 2017 Classification of Seizure Types Expanded Version

**Focal Onset**
- **Aware**
  - Motor Onset: automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic
  - Nonmotor Onset: autonomic, behavior arrest, cognitive, emotional, sensory

- **Impaired Awareness**
  - focal to bilateral tonic-clonic

**Generalized Onset**
- Motor:
  - tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms
  - Nonmotor (absence):
    - typical, atypical, myoclonic, eyelid myoclonia

**Unknown Onset**
- Motor:
  - tonic-clonic, epileptic spasms
  - Nonmotor:
    - behavior arrest

Unclassified

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1. Fisher et al., 2017
2. Tonic-clonic seizures may be accompanied by atonic episodes.
3. Includes absence seizures, tonic-clonic seizures, and other seizures.
Figure 2: Seizures according to mode of onset

**Mode of Onset**

- **Generalised:**
  - Originates at some point within the brain, and rapidly engage bilaterally distributed networks, which can be subcortical or cortical structures.

- **Focal:**
  - Seizures that originate in networks limited to one hemisphere.
  - May arise from either subcortical structures or neocortex.
  - Descriptors of focal seizures to describe an event more precisely:
    - Without impairment of consciousness or awareness.
    - Involving subjective sensory or psychic phenomena.
    - With impairment of consciousness or awareness, or dyscognitive.
    - Evolving to a bilateral tonic-clonic seizure.

- **Other:**
  - Seizure types where it remains unclear whether onset is focal, generalized, or perhaps either e.g., epileptic spasms.
  - “Unclassified” used in cases with inadequate information for accurate diagnosis & classification.
Figure 3: Classification according to the aetiology of epilepsy

**GENETIC:**
*Epilepsy is the direct result of a known or presumed genetic defect.*

*Seizures are the core symptom of the disorder.*

e.g., childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy

**STRUCTURAL:**

**Congenital**
- e.g., cortical dysplasia, tuberous sclerosis

**Acquired**
- e.g., stroke, trauma, infection, immune-based

**METABOLIC:**
- e.g., mitochondrial disorders

**UNKNOWN:**
2 Neuropsychiatry and Epilepsy

There is a bidirectional relationship between epilepsy and neuropsychiatric conditions. Around 30-50% people with epilepsy experience psychiatric, behavioural, or social difficulties (Lin et al., 2014). Irrespective of the cause and duration, any form of epilepsy can have neuropsychiatric implications. Longer standing epilepsy with frequent uncontrolled seizures and polypharmacy is more likely to have neuropsychiatric sequelae. Co-morbid substance use and pre-existing psychiatric disorders are also significant factors.

The site of the brain lesion is important in determining the possible neuropsychiatric features with temporal lobe involvement often manifesting with such features. Parietal and Occipital lobe seizures are far less common but are an important consideration especially when there are atypical ictal features. Parietal lobe seizures – can be associated with hallucinations, sensory & motor symptoms. Occipital lobe seizures – can include hallucinations, visions, vision loss and oculomotor symptoms.

Figure 4: Epilepsy syndromes associated with neuropsychiatric symptoms

*Abbreviations:
SMA= Supplementary motor area; TLE= Temporal lobe epilepsy
2.1. Psychiatric symptoms related to ictal phases

It is useful to consider neuropsychiatric symptoms related to epilepsy into:

> Pre-ictal, ictal, post ictal, and interictal phenomena (Table 1).

It helps to determine the primary intervention that is required. Pre-ictal, post-ictal and ictal phenomena require improved seizure control.

Inter-ictal neuropsychiatric symptoms are not directly related to the seizure and may thus require additional psychiatric treatment for the specific psychiatric symptom that has emerged.

For each “phase” of seizure phenomenon, it can be helpful to consider the broad categories of Neuropsychiatric Symptoms: Cognitive, Anxiety, Mood / Affective, Psychotic, Sleep / Vegetative.
Table 1: Psychiatric symptoms related to ictal phases

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Anxiety</th>
<th>Mood</th>
<th>Psychosis</th>
<th>Sleep &amp; Vegetative</th>
<th>Other / Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ictal “prodrome” (hours to days)</td>
<td></td>
<td>Irritability</td>
<td>Depression</td>
<td>Hallucinations - often incl non auditory</td>
<td></td>
<td>Headache Malaise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysphoria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ictal (including aura)</td>
<td>Ictal anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relatively Stereotyped</td>
</tr>
<tr>
<td>Post-ictal</td>
<td>Confusion common (&lt;30min)</td>
<td>Anger and aggression common</td>
<td>Preceding lucid period (24 hrs), abrupt onset, agitation, behavioural disturbance</td>
<td>Drowsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-ictal</td>
<td>Mild attention, executive function, or memory dysfunction. Can be progressive over years</td>
<td>Anxiety common (agora-phobia, GAD, social)</td>
<td>Depression common (irritability &amp; somatic)</td>
<td>SCZ like psychosis: Associated with recurrent postictal psychosis</td>
<td>Hyposociality common (medication, TLE)</td>
<td>Personality changes controversial</td>
</tr>
</tbody>
</table>

Cogn imp, cognitive impairment; Esp, especially; GAD, generalised anxiety disorder; SCZ, schizophrenia; TLE, Temporal lobe epilepsy
3 Differential diagnosis of epilepsy

It is important to consider a differential diagnosis for seizure like activity (Figure 5). A notable differential diagnosis for the mental health practitioner is psychogenic non epileptic seizures (PNES).

**Figure 5: Mimickers of epilepsy**

![Mimickers of epilepsy diagram]

3.1 Psychogenic non epileptic seizures (PNES)

PNES is an important consideration when any of the following are present:
- atypical seizures,
- associated emotional triggers preceding the seizure,
- poor response to adequate anti-epileptic treatment,
- pre-existing psychiatric history, or
- childhood trauma.

It is more common in the 20-40 years age group, with a female to male ratio of 3:1. Care needs to be taken not to over-diagnose this condition. Epilepsy can and does co-exist with PNES (approx. 30%). Inter-specialty input between neurology and psychiatry is the ideal. The gold standard investigation for diagnosis is 24-hour video electroencephalogram (EEG) monitoring. A multidisciplinary approach is vital, especially psychological interventions. Co-morbid psychiatric conditions should also be treated.
**Table 2: Features that can help differentiate epileptic vs psychogenic seizures**  
(adapted from R Duncan)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Epileptic</th>
<th>Psychogenic non epileptic seizures (PNES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Usually brief (&lt; 1-2 min)</td>
<td>Usually &gt; 2 mins</td>
</tr>
<tr>
<td>Eyes</td>
<td>Usually open</td>
<td>Often closed</td>
</tr>
<tr>
<td>Motor activity</td>
<td>Stereotyped, builds &amp; progresses, synchronized</td>
<td>Variable, wax &amp; wanes, pelvic thrusting, rolling side to side</td>
</tr>
<tr>
<td>Vocalization</td>
<td>Uncommon</td>
<td>May occur</td>
</tr>
<tr>
<td>Prolonged ictal atonia</td>
<td>Very rare</td>
<td>May occur</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Common in convulsive seizures</td>
<td>Less common</td>
</tr>
<tr>
<td>Autonomic signs</td>
<td>Cyanosis &amp; tachycardia common in major convulsions</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Postictal symptoms</td>
<td>Headache common, confusion, drowsiness</td>
<td>Headache rare, can awaken &amp; be fully orientated.</td>
</tr>
</tbody>
</table>

4 Assessment of Epilepsy and Neuropsychiatric Aspects

Epilepsy is a neurological condition and the diagnosis should ideally be made by a neurologist. The role of the psychiatrist or mental health practitioner is to take a thorough history in cases of suspected PNES and other presentations that on the surface appear to be atypical of an epileptic seizure. The history must include: The medical and surgical history especially neurosurgery, illicit and over the counter drug use, family history, and current and past medication use. Collateral information is essential and taking video footage of the episodes should be encouraged and brought to subsequent consultations where possible. Appropriate blood investigations should be done, including full blood count (FBC), urea, electrolytes and creatinine (UCE), liver function test (LFT), thyroid function, HIV, and syphilis serology. EEG should be done where deemed necessary e.g. when the diagnosis is unclear. Neuroimaging may be warranted especially with focal seizures. Magnetic resonance imaging (MRI) is more sensitive to finding pathology but availability and cost limit access to this modality. Very often the best special investigation in a case of suspected epilepsy is obtain further collateral account of the seizure and related events.
5 General management principles
Optimise seizure control, refer to neurology for further workup and medication adjustment as indicated. Awareness of the commonly used antiepileptic drugs (AEDs) and their neuropsychiatric sequelae is important (see Table 3). Prescribers should keep potential drug-drug interactions with AEDs in mind when choosing psychotropic medication.

*Table 2: Commonly prescribed AEDs & their neuropsychiatric implications*
(adapted from S Karceski)

<table>
<thead>
<tr>
<th>Medication: Sodium Valproate (metabolised to valproic acid in GIT)</th>
<th>Mechanism of action</th>
<th>Type of epilepsy (Indication)</th>
<th>Neuropsychiatric indications</th>
<th>NB Drug-drug interactions</th>
<th>Neuropsychiatric Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indirectly increases GABA</td>
<td>Generalised tonic clonic (GTC); Absence</td>
<td>Bipolar disorder (for mania &amp; depression); Aggression, agitation</td>
<td>Valproate can increase levels of TCAs, lamotrigine, quetiapine OCP co-admin can lower Na Valproate levels</td>
<td>Tremor, parkinsonism associated with cognitive decline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication: Lamotrigine</th>
<th>Mechanism of action</th>
<th>Type of epilepsy (Indication)</th>
<th>Neuropsychiatric indications</th>
<th>NB Drug-drug interactions</th>
<th>Neuropsychiatric Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>May affect neurons that synthesise glutamate &amp; aspartate</td>
<td>Focal onset seizures; GTC seizures</td>
<td>Bipolar depression; impulsivity and behavior symptoms in borderline PD</td>
<td>Enzyme inducers (phenytoin, carbamazepine, phenobarbital, estrogen-containing OCPs, rifampin, protease inhibitors) can lower levels of lamotrigine</td>
<td>Neurotoxic side effects: dizziness and somnolence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication: Carbamazepine</th>
<th>Mechanism of action</th>
<th>Type of epilepsy (Indication)</th>
<th>Neuropsychiatric indications</th>
<th>NB Drug-drug interactions</th>
<th>Neuropsychiatric Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Binds to voltage dependent Na channels</td>
<td>Focal and generalized seizures</td>
<td>Bipolar disorder and chronic pain syndromes e.g., trigeminal neuralgia.</td>
<td>Potent and broad-spectrum inducer of the CYP system</td>
<td>Sexual dysfunction, drowsiness, dizziness, blurred or double vision, lethargy, &amp; headache</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>Binds to voltage dependent Na channels</td>
<td>Focal &amp; generalized seizures, status epilepticus</td>
<td>Nil</td>
<td>Potent inducer of CYP system</td>
<td>Confusion, slurred speech, double vision, ataxia, and neuropathy (with long-term use)</td>
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<tr>
<td><strong>Levetiracetam</strong></td>
<td>Unknown, in animals binds to the synaptic vesicle protein SV2A</td>
<td>Adjunctive therapy for focal-onset seizures</td>
<td>Nil</td>
<td>Metabolism not related to CYP system</td>
<td>Fatigue, somnolence, dizziness</td>
</tr>
</tbody>
</table>

Co-admin, co-administration; CYP, Cytochrome P450; GABA, Gamma aminobutyric acid (GABA); GIT, gastrointestinal tract; NA, sodium; NB, important; OCP, oral contraceptive pill; PD, personality disorder; SV2A, Synaptic vesicle glycoprotein 2A; TCAs, tricyclic antidepressants
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Karceski S. Initial treatment of epilepsy in adults Uptodate.com