Neuropathophysiology of Epilepsy and Psychiatric Comorbidity & Diagnosis and Management of Non-Epileptic Attack Disorders

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Psychiatric Disorders associated with Epilepsy

• Very Common:

  • Depression 15 – 60%
  • Anxiety > 50%
  • Psychosis 5 – 20%
  • Nonepileptic Behavioural events 1 – 2%
Psychiatric comorbidity in epilepsy: A population-based analysis

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### Table 1. Psychiatric comorbidity in people with epilepsy and the general population

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>No epilepsy (N = 36,727) (95% CI)</th>
<th>Epilepsy (N = 253) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder (Lifetime)</td>
<td>10.7 (10.2–11.2)</td>
<td>17.4 (10.0–24.9)</td>
</tr>
<tr>
<td>Mood disorder (Lifetime)</td>
<td>13.2 (12.7–13.7)</td>
<td>24.4 (16.0–32.8)</td>
</tr>
<tr>
<td>Mood disorder (12 month)</td>
<td>5.2 (4.9–5.5)</td>
<td>14.1 (7.0–21.1)</td>
</tr>
<tr>
<td>Anxiety disorder (Lifetime)</td>
<td>11.2 (10.8–11.7)</td>
<td>22.8 (14.8–30.9)</td>
</tr>
<tr>
<td>Anxiety disorder (12 month)</td>
<td>4.6 (4.3–4.9)</td>
<td>12.8 (6.0–19.7)</td>
</tr>
<tr>
<td>Mood/anxiety disorder (12 month)</td>
<td>8.0 (7.6–8.5)</td>
<td>19.9 (12.3–27.4)</td>
</tr>
<tr>
<td>Mood/anxiety disorder/dysthymia (lifetime)</td>
<td>19.6 (19.0–20.2)</td>
<td>34.2 (25.0–43.3)</td>
</tr>
<tr>
<td>Panic disorder/agoraphobia (Lifetime)</td>
<td>3.6 (3.3–3.9)</td>
<td>6.6 (2.9–10.3)</td>
</tr>
<tr>
<td>Panic disorder/agoraphobia (12 month)</td>
<td>2.0 (1.8–2.2)</td>
<td>5.6 (1.9–9.2)</td>
</tr>
<tr>
<td>Suicidal ideation (lifetime)</td>
<td>13.3 (12.8–13.8)</td>
<td>25.0 (17.4–32.5)</td>
</tr>
<tr>
<td>Any mental health disorder (12 month)</td>
<td>10.9 (10.4–11.3)</td>
<td>23.5 (15.8–31.2)</td>
</tr>
<tr>
<td>Any mental health disorder (lifetime)</td>
<td>20.7 (19.5–20.7)</td>
<td>35.5 (25.9–44.0)</td>
</tr>
</tbody>
</table>
Depression and Epilepsy

Fig. 1. Association between major depression and the development of medical and neurological disorders.
Depression in epilepsy is associated with lack of seizure control

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c Department of Statistics, University of California, Davis, CA, USA
Prevalence ratio for patients reporting no seizures in the past 6 months versus patients reporting any seizure.
• Depression is more common if seizures are uncontrolled

• Rates of depression increase with the number of AEDs independently of seizure control
More Complicated

• Possible biological link

• A personal history, or a family history of depression prospectively increases the risk of epilepsy by 3 – 7 times (5 population studies)
Antidepressants and Epilepsy

• Psychiatrists and GPs may be concerned that antidepressants will exacerbate seizures
  • What’s the evidence
  • Almost entirely based on overdose data

• SSRI have been shown to reduce epileptogenicity in animal studies
• Citalopram and Fluoxetine have shown possible AE in 3 open trials
• Imipramine has RCT evidence of anticonvulsant effect in absence seizures

• Plus indirect RCT evidence
  • In a meta-analysis of RCTs of SSRI in depression, the SSRI patients had 69% fewer seizures
Antidepressants and Epilepsy

• Are anti-epileptics any good as antidepressants?
  • No

• Is depression less common in patients on different AEDs
  • There is no difference in rates of depression between different drugs except for Levetiracetam
Psychosis and Epilepsy

Evidence for Shared Susceptibility to Epilepsy and Psychosis: A Population-Based Family Study
Mary C. Clarke, Antti Tanskanen, Matti O. Hutunen, Maurice Clancy, David R. Cotter, and Mary Cannon

• Finish population of 23,196
  • 203 had epilepsy
  • Epilepsy increased the risk of psychosis several-fold
  • Family history of epilepsy approximately doubled the risk of psychosis and vice versa
Basic treatment principles for psychotic disorders in patients with epilepsy

Vulnerable brain
(neurodevelopmental or acquired abnormality)

Cryptic insults

Epilepsy (?temporal lobe)

Seizures

Psychosocial factors

Lobectomy

Drugs

Cellular & molecular changes post-seizures

Excitation/inhibition imbalance

Postictal psychosis

Brief interictal psychosis

Repeat episodes

Neurochemical change

Inhibition

Schizophrenia-like psychosis
Basic treatment principles for psychotic disorders in patients with epilepsy

**A**

![Diagram A]

**B**

![Diagram B]

**Overshooting hyperpolarization?**

**Limbic status epilepticus (or aura continua)?**

Basic treatment principles for psychotic disorders in patients with epilepsy, Volume: 54, Issue: s1, Pages: 19-33, First published: 04 March 2013, DOI: (10.1111/epi.12102)
Interictal Psychosis

• Psychotic episodes in patients with epilepsy that occur without direct relation to seizures

• Usually indistinguishable from schizophrenia

• Onset approximately 15 years after epilepsy

• Focal epilepsies > generalized epilepsies
  • TLE > other focal epilepsies
  • No laterality
  • No other predisposing factors
Interictal psychotic episodes in epilepsy: Duration and associated clinical factors
Postictal Psychosis

• Less schizophreniform, more mania-like

• Following a seizure cluster
• Lucid interval
• Suicide risk
• Bitemporal pathology
• Malformations
• Family history of mood disorder
Delusions, illusions and hallucinations in epilepsy: 2. Complex phenomena and psychosis

Brent Elliott, Eileen Joyce, Simon Shorvon*

<table>
<thead>
<tr>
<th>Study</th>
<th>EEG</th>
<th>Electrophysiology</th>
<th>Psychopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wieser et al. (1985)</td>
<td>SEEG</td>
<td>Temporal lobe status epilepticus.</td>
<td>Stickiness, aggressivity, dysphoria and depression</td>
</tr>
<tr>
<td>Trimble (1991)</td>
<td>Sphenoidal EEG</td>
<td>Frequent sharp waves with phase reversals on the right.</td>
<td>Paranoid schizophreniform psychosis</td>
</tr>
<tr>
<td>Takeda et al. (2001)</td>
<td>SEEG</td>
<td>Left amygdala discharges becoming almost continuous.</td>
<td>Internal dialogue with the voices of her parents, restless, anxious and fearful</td>
</tr>
<tr>
<td>Kanemoto (1997)</td>
<td>SEEG</td>
<td>Clear cut epileptiform discharge in left amygdalo-hippocampal region.</td>
<td>Capgras syndrome</td>
</tr>
<tr>
<td>Kristensen and Sindrup (1978)</td>
<td>Spehnoidal EEG</td>
<td>Temporal medio-basal spike foci.  More frequent and more likely bilateral than in non-psychotic controls.</td>
<td>Paranoid/hallucinatory interictal psychosis</td>
</tr>
</tbody>
</table>
• Psychotic symptoms vs psychosis

• A large body of evidence links symptoms that might be described as psychotic with ictal epileptiform discharges involving specific brain structures

• Elation, depression, paranoia, fear, auditory hallucinations, visual hallucinations, dissociation

• So is the whole psychosis thing just ‘seizures’?
Psychotic features in seizures: what do seizure discharges do to the brain?

1. They stimulate it, intensely and indiscriminately.

2. They inhibit it, producing dysfunction of local and distant parts of the brain.

3. Inhibition is usually most near the seizure onset zone, but can be widespread …..
Non-Epileptic Seizures aka Pseudo-seizures or Psychogenic Non-Epileptic Seizures
Are involuntary behavioural responses to internal or external triggers that superficially resemble epileptic seizures but are not associated with the abnormal electrical activity associated with the latter.

Somatoform conversion disorder manifesting as paroxysmal events not associated with electroencephalographic (EEG) epileptiform correlates, that have psychological underpinnings.
Epidemiology

- Approximately one in five patients seen in seizure clinics are diagnosed with PNES
- 75% are female
- 10% also have epilepsy
  - PNES are almost invariably preceded by the manifestation of epileptic seizures
- 40% (or so) have antecedent sexual trauma
- Most frequently start in late adolescence or early adulthood (but range very wide)
- Patients with intellectual disabilities or head injuries may be increased risk
Types of Pseudoseizure

- Convulsive  61%
- Swoon  30%
- Absence or
- Pseudomyoclonic  <10%

*n=177 Selkirk M, Duncan R, Oto M, Pelosi A. Clinical differences between patients with nonepileptic seizures who report antecedent sexual abuse and those who do not. Epilepsia 2008;49:1446-1450*
Features

- Long duration
- Occurrence from apparent sleep with EEG-verified wakefulness
- Fluctuating course
- Asynchronous movements
- Pelvic thrusting
- Side-to-side head or body movements
- Closed eyes during episode
- Ictal crying
- Memory recall
- Absence of postictal confusion
Treatment

• Make an accurate diagnosis

• Cognitive behavioural therapy

• Addressing any psychiatric comorbidities
From: Multicenter Pilot Treatment Trial for Psychogenic Nonepileptic Seizures A Randomized Clinical Trial


### Table 2. Within-Treatment Condition Monthly Seizure Count Change

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, No.</th>
<th>Slope (SE) [95% CI]</th>
<th>$T_{438}$</th>
<th>P Value</th>
<th>Posttreatment/Pretreatment Ratio of Seizures, Mean (SE) [95% CI]</th>
<th>Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT-ip</td>
<td>9</td>
<td>-0.72 (0.3) [-1.3 to -0.2]</td>
<td>-2.95</td>
<td>.01</td>
<td>0.49 (0.1) [0.28 to 0.84]</td>
<td>51.4</td>
</tr>
<tr>
<td>CBT-ip with sertraline</td>
<td>9</td>
<td>-0.90 (0.3) [-1.6 to -0.2]</td>
<td>-2.69</td>
<td>.008</td>
<td>0.41 (0.1) [0.21 to 0.79]</td>
<td>59.3</td>
</tr>
<tr>
<td>Sertraline</td>
<td>9</td>
<td>-0.31 (0.2) [-0.6 to 0.03]</td>
<td>-1.78</td>
<td>.08</td>
<td>0.74 (0.1) [0.52 to 1.03]</td>
<td>26.5</td>
</tr>
<tr>
<td>Treatment as usual</td>
<td>7</td>
<td>-0.40 (0.3) [-1.0 to 0.2]</td>
<td>-1.32</td>
<td>.19</td>
<td>0.67 (0.2) [0.37 to 1.21]</td>
<td>33.8</td>
</tr>
</tbody>
</table>

Abbreviation: CBT-ip, cognitive behavioral therapy informed psychotherapy.  

*Statistically significant differences.*
Monthly Trajectory of Seizure Counts by Treatment Condition Lines indicate functions of the mean weekly seizure count; shaded areas, variation corresponding to each line (treatment arm). Cognitive behavioral therapy informed psychotherapy (CBT-ip) with sertraline, P = .008; CBT-ip only, P = .01; sertraline only, P = .08; and treatment as usual, P = .19. Median time in the trial was 15 weeks, with a median range from 14 weeks in the sertraline group to 17 weeks in the group receiving CBT-ip only and the group receiving CBT-ip with sertraline.
Summary

• Depression is common in patients with epilepsy and in particular those patients with difficult to control seizures
• There is a complicated relationship between epilepsy/seizures and psychosis

• Psychogenic Non-Epileptic Seizures are a relatively common neurological illness that requires collaborative treatment.
I danced like no one was watching but someone was watching, thought I was having a seizure and called an ambulance.