Psychiatric Comorbidity in Epilepsy

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Psychiatric Disorder in Epilepsy

◊ First organized description from Falret & Morel (1860)
  • "The periodicity of mental changes and prominence of outbursts of anger & fury"

Psychiatric Comorbidity of PWE

• Negative impact on response to treatment
• Risk factor for poor quality of life
• Increase burden and cost on healthcare services
• Remained underrecognized and undertreated by the majority of clinicians

Prevalence of Psychiatric Comorbidity

<table>
<thead>
<tr>
<th>DSM-defined diagnosis</th>
<th>Prevalence rate (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood disorder</td>
<td>24 – 75%</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>10 – 25%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2 – 7%</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1 – 2%</td>
</tr>
</tbody>
</table>

Jones R et al, Functional Neurology 2010

Relationship between Psychiatric disorder and Epilepsy

• Psychiatric disorders caused by the seizures: ictal, postictal, and interictal disorders
• Epileptic and psychiatric disorders caused by common brain pathology
• Epileptic and psychiatric disorders coexist in the same patient but are not causally related

Mechanism of Comorbidity

• Common neuropathology/epileptic predisposition
• Developmental disturbance
• Lead or sub-lead neurophysiological effects
• Alteration of receptor sensitivity
• Secondary endocrinological alterations
• Primary, independent psychiatric illness
• Consequence of medical or surgical treatment
• Consequence of psychosocial burden of epilepsy
Classification of Psychiatric Disorders Associated with Epilepsy by Fenton (1981)

1. Disorders clearly attributable to the brain disorder causing the epilepsy
   - Learning disability
   - Chronic organic brain syndromes
   - Focal brain disease

2. Disorders strictly related in time to seizure occurrence
   - Preictal - premonitory
   - Ictal - psychiatric manifestations of seizure activity (aura, automatism, etc. status, FLE)
   - Postictal - psychiatric abnormalities occurring in the immediate postictal period

3. Interictal psychiatric disorders
   - Childhood disorders
   - Neuroses
   - Psychoses
   - Personality disorder
   - Dementia

Classification of Neuropsychiatric Disorders in Epilepsy
ILAE Commission on Psychobiology of Epilepsy (2006)

1. Psychopathology as presenting feature of epileptic seizures
2. Interictal psychiatric disorder that are specific to epilepsy
   - Cognitive dysfunction
   - Psychosis of epilepsy
   - Affective–somatomotor (dysphoric) disorders of epilepsy
3. Personality disorder
4. Other relevant conditions
   - Seizures related to EEG change - focused normalization
   - AED induced psychiatric disorders

Effects of AED

Depression in Epilepsy

- Prevalence ranged from 20-55% in recurrent seizure, 3-9% in controlled epilepsy
- Jacody (1996) reported lifetime prevalence = 29%, comparing to 16% in DM, 17% in asthma, 8.7% in healthy respondents
- Impacts: Used more health resources, poor QoLs, 5 time greater risk of suicide

Prevalence of Depression among PWE

A Bidirectional Relation

- Traditional view: Consequence or Complication
- Recent finding: Epilepsy increase risk for depression,
  Depression increase 3-7 fold risk for epilepsy
- Animal model
  - Increase anxiety and depressive behavior preceding seizure in Transgenic rats
  - Worsening seizure with substances interfere with synthesis or release of NE, 5HT
- Treatment with NE, 5HT agent blocked seizure
A Bidirectional Relation

- Recent finding: Human studies
  - Decrease bingeing of HT1A of PET scan in both disorder
  - Significant drop in seizure in 3 trial of SSRIs in patients with treatment-resistant epilepsy.
  - Serotonin’s anticonvulsant effect mediated via inhibition of voltage-gated ion channels, effect on GABA and glutamate receptors, neurosteroid synthesis.

Dysphoria in epilepsy

- Kraepelin(1923) stated "Periodic dysphorias represent the most common psychiatric dis. in epilepsy, characterized by irritability with or without outbursts of fury. Accompanied by depressed mood, anxiety, headache & insomnia."
- Mulder&Dally (1952) - reactive depression
- Bett (1974) - endogenous presentation
- Mendez (1986) - few anxiety, guilt, hopelessness, low self-esteem, but more psychotic symptoms

Etiology of Depression in epilepsy

- Forced normalization
- AED induced depression: vigabatrin, tiagabine, topiramate, phenobarbital, levetiracetam
- Laterality hypothesis: connectivity of mesial temporal lobe to frontal lobe; left TLE (consequence of seizure)
- Endocrine & metabolic consequence from seizure
- Psychological factors: Unpredictability & uncontrollability; learned helplessness, burden of normality

Risk factors for depression

- Gender: Male > female
- Sinistrality: left-handed PWE (indicated early brain injury)
- Related neurological condition: MS, CVD, dementia, head injury
- Genetic Family history of depression, suicide
- Amygdala enlargement and hippocampal atrophy
- Past history of behavioral disturbance in childhood, neurosis
- Patients with learning disability, low IQ
- Late-onset epilepsy, CPS, MTS, TLE

Depression in PWE

- DSM-IV Symptom Dimensions of a Major Depressive Episode
  - > 50% have atypical manifestation: depression, irritability, anxiety
  - Anhedonia is the better marker for depression
  - Symptoms may confound with physical side, medication SE
  - Classified as: interictal vs periictal/preictal, ictal, post-ictal
  - Depression can be iatrogenic effect associated with the introduction or discontinuation of certain AEDs, complication of surgery
  - Some patients have subsyndromic form of depression
  - Some patients have comorbid anxiety: predicted higher risk of suicide and treatment-resistant depression
Post-ictal depression

<table>
<thead>
<tr>
<th>Postictal symptom of depression</th>
<th>Frequency (N = 100)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor frustration</td>
<td>36</td>
<td>24 (0.5–108)*</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>33</td>
<td>24 (0.1–148)</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>25</td>
<td>24 (1.0–108)</td>
</tr>
<tr>
<td>Helplessness</td>
<td>31</td>
<td>24 (1.0–108)</td>
</tr>
<tr>
<td>Crying hours</td>
<td>26</td>
<td>6 (0.1–108)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>13</td>
<td>24 (1.0–240)</td>
</tr>
<tr>
<td>Irritability</td>
<td>30</td>
<td>24 (0.5–108)</td>
</tr>
<tr>
<td>Guilt</td>
<td>23</td>
<td>24 (0.3–240)</td>
</tr>
<tr>
<td>Self-deprecation</td>
<td>27</td>
<td>24 (1.0–120)</td>
</tr>
</tbody>
</table>

a = Median (Range)

Source: Kanner Am et al. Epilepsy & Behavior 2010

Dietrich Blumer’s interictal dysphoric disorder

- Patients with refractory epilepsy, esp. TLE
- Short duration, lasts hours to 3 days, attenuates in premenstrual period
- Increase risk of sudden, unexpected suicide attempts, interictal psychosis
- 3 of the followings (Depressive-somatiform symptoms, affective symptoms)

<table>
<thead>
<tr>
<th>Labile depressive symptoms</th>
<th>Labile affective symptoms</th>
<th>Specific symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive mood</td>
<td>Manic</td>
<td>Psychotic irritability</td>
</tr>
<tr>
<td>Anergia</td>
<td>Anxiety</td>
<td>Euphoric moods</td>
</tr>
</tbody>
</table>

Source: Blumer D et al Harv Rev Psychiatry 200

Assessment

- Structured interviews:
  - The Structured Clinical Interview for DSM IV Axis I Disorder (SCID)
  - The Mini International Neuropsychiatric Interview (MIND)
  - Hamilton Rating Scale for Depression (HRSD, HAM-D)
- Screening psychometric test:
  - Beck Depression Inventory (21 items)
  - Center for Epidemiology Studies-Depression Scale (CES-D)
  - The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

Management of Depression

- Pre-ictal and ictal depression: reduce seizure frequency
- Benzodiazepine, behavior intervention may abort or prevent the development of the symptoms
- Treatment with antidepressants involves 3 major issues
  - Effect of antidepressants on seizure threshold
  - Antidepressant-anticonvulsant interaction
  - Efficacy of antidepressant in PWE

Source: Blumer D et al Harv Rev Psychiatry 200

Management of depression in epilepsy

- Pre-ictal and ictal depression: reduce seizure frequency
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Source: Blumer D et al Harv Rev Psychiatry 200
Prevention of depression

- Iatrogenic depressive episodes are common
- Psychiatric adverse events of AED related with past psychiatric history and/or family psychiatric history.
- Prevention strategy:
  1. Avoid introduce of an AED with negative psychotropic properties
  2. Monitor the discontinuation of an AED with mood-stabilizing properties: valproate, carbamazepine, lamotrigine...
  3. Adjust doses of antidepressants when introducing AED with enzyme-inducing properties
  4. Assess psychiatric premorbidity of PWE before epilepsy surgery to avoid depression in the first 6 months (20-30%)

Kanner AM. Epilepsia 2013

Psychiatric risk of AED

- Patient's premorbid psychology: AED Possible SE
  - Agitation
  - Insomnia, anxiety, hypomania
  - Paranoia
  - Major depression
  - Antidepressive
  - Seizure


Effects of ATD in PWE

- Cardamone L et al. British J of Pharmacology 2013
- Efficacy of ATD in PWE
  - Schimtz B. Epilepsia 2006

- psychiatric risk of AED
  - Patient's premorbid psychology: AED Possible SE
    - Agitation
    - Insomnia, anxiety, hypomania
    - Paranoia
    - Major depression
    - Antidepressive
    - Seizure

Other treatment
- AED - as mood stabilizer (lamotrigine, valproate, carbamazepine)
- US FDA alert for increase risk of suicide with AEDs as a class in 2008, based on meta-analysis
- Vagus nerve stimulation (VNS), ECT and rTMS - limited data in epilepsy
- Physical activity for mild depression
- Psychological treatment: Relaxation therapy, CBT, yoga

Anxiety Disorder in PWE
- Anxiety may be more common than depression and equally disabling
- 11-25% in generally, >50% in some specialist setting
- Significant predictor of reduced health-related QoL
- Relative frequent in treatment resistant epilepsy
- Associated with a poor response to pharmacotherapy
- Tend to comorbid with depressive disorder
- PWE can experience more than 1 anxiety disorder
- Increase risk of suicide

Anxiety Disorder in PWE
- Generalized anxiety disorder: fear of future seizure, disease progression, complication
- Panic attack and panic disorder: ictal anxiety/fear
- Phobia: agoraphobia, social phobia
- Obsessive compulsive disorder: aura (forced thinking)

Panic Attack vs. focal seizure

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Primary panic attack</th>
<th>Focal seizure with ictal fear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>Alert</td>
<td>Alert fear may progress to impaired</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;10 min</td>
<td>0.5 – 2 min</td>
</tr>
<tr>
<td>Flushing</td>
<td>Very rare</td>
<td>Very infrequent</td>
</tr>
<tr>
<td>Aggravation</td>
<td>Very common</td>
<td>Common with progression to CPS</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>Common, severity associated</td>
<td>Common, severity not associated</td>
</tr>
<tr>
<td>Anticipatory anxiety</td>
<td>Common, severity not associated</td>
<td>Common, severity not associated</td>
</tr>
<tr>
<td>Anterior EEG</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Interictal EEG</td>
<td>Normal</td>
<td>Often abnormal</td>
</tr>
<tr>
<td>MRI of temporal lobe</td>
<td>Usually normal</td>
<td>Often abnormal</td>
</tr>
</tbody>
</table>

Vazquez B et al Epilepsy Behav 2003

Risk Factors for Anxiety
- Seizure frequency and perception of danger
- Late life onset
- Focal (TLE, Left) > generalized epilepsies
- Chronic refractory seizure disorders

Neurobiology Mechanism
- Amygdala → anxiety, panic disorder, ictal fear
- Seizure arising in ant. cingulate, orbitofrontal cortex
- Abnormal function of GABA-A receptors (some AED have anxiolytic properties)
Anxiety symptoms and seizure

- Comorbid anxiety disorder
- Ictal phenomenon
- Postictal phenomenon
- Interictal phenomenon

Anxiety Symptoms and AED

- AED can exacerbate anxiety / have anxiolytic effects
- History of psychiatric disorder increased vulnerability to psychiatric side effects of AED
- AEDs with glutamatergic mechanism cause activation
  AEDs enhance GABAergic alleviate anxiety.

Treatment of Anxiety in PWE

- Psychoeducation and support
- Counselling, CBT
- Medication: antidepressant (SSRIs, TCA), BZD
- AED with anxiolytic potential: barbiturate, CBZ, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabin, valproate,

Risk of seizure with drugs prescribed for anxiety disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (5% or higher risk of seizure)</td>
<td>9</td>
</tr>
<tr>
<td>Chlorpromazine (high dose)</td>
<td>1</td>
</tr>
<tr>
<td>Medium risk (0.5% or higher risk of seizure)</td>
<td>0.5</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
</tr>
<tr>
<td>Biperidone</td>
<td>1</td>
</tr>
<tr>
<td>Clozapine (high dose)</td>
<td>1</td>
</tr>
<tr>
<td>Low risk (0.5% or lower risk of seizure)</td>
<td>0.3</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.1</td>
</tr>
<tr>
<td>Trazodone</td>
<td>0.3</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Psychosis in PWE

Categorized in relation to seizures or treatment:
- Ictal psychosis
- Postictal psychosis
- Interictal psychosis
- Forced normalization/alternative psychosis
- De novo psychosis following epileptic surgery

Logsdail & Toone Operational Criteria for PIP

1. Onset of confusion or psychosis within 1 week of return of apparent normal function
2. Duration of 1 day to 3 months
3. Mental state characterized by:
   a. Clouding of consciousness, disorientation, delirium
   b. Delusion or hallucination in clear consciousness
   c. A mixture of a and b
4. No evidence of factors which may contribute to the abnormal mental state:
   a. AED toxicity
   b. A previous history of interictal psychosis
   c. EEG evidence of status epilepticus
   d. Recent history of head injury or alcohol drug intoxication
Annual Incidence of new cases of psychosis

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Lin et al. (1991)</td>
<td>0.17%</td>
</tr>
<tr>
<td>Ohara et al. (1995)</td>
<td>0.10%</td>
</tr>
<tr>
<td>Bridger et al. (1998)</td>
<td>0.10%</td>
</tr>
<tr>
<td>Takahara et al. (2002)</td>
<td>0.12%</td>
</tr>
</tbody>
</table>

Schizophrenia in general population

| World Health Organization (1992) | 0.22% | Median value (15-54 years of age) |

Kanemoto K. et al Ther Adv Neurol Disord. 2012

Pathophysiology of Psychosis in PWE

Age at psychosis onset on PWE and Schizophrenia

Schizophrenia

Age (years old)

20

25

30

35

Kanemoto K. et al Ther Adv Neurol Disord. 2012