Epilepsy and Psychosis: An Overview

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Epilepsy and Psychosis

• Psychiatric disorders are 4x more common in adults with childhood-onset epilepsy regardless of whether still on AEDs
• Psychosis occurs in > 5% people with epilepsy
• Schizophrenia:
  – 1% of the population and
  – 1% of chronic migraine suffers
Epilepsy and Psychosis

• Peri-ictal
  – Ictal (non convulsive SE)
  – Post-ictal
• Inter-ictal
  – Acute interictal psychosis
    • Alternative Psychosis (Forced normalisation)
  – Chronic interictal psychosis (SLPE)
  – Schizophrenia/depressive psychosis
• Iatrogenic
  – Medication
    • Alternative Psychosis (Forced normalisation)
  – Surgery
Ictal Psychosis

- Psychotic symptoms occurring as part of the seizure
- Prolonged – *non convulsive status epilepticus*
- Affective/ behavioural symptoms (agitation)
- Perceptual experiences (delusions, visual hallucinations)
- Automatisms (oral)
- Eyelid fluttering/ myoclonus
Ictal Psychosis

- Consciousness is often impaired (not with simple partial status) – may fluctuate
- Followed by amnesia
- Diagnosis – EEG – epileptiform (focal or bilateral) often with slow background activity
  – may be normal with simple partial status
- Treatment – AEDs
Post Ictal Psychosis: Logsdail and Toone, 1988

- Onset of confusion within 1 week of the return of normal mental function
- Duration: 1 day – 3 months
- Mental state:
  - clouding of consciousness, disorientation or delirium,
  - clear consciousness
  - or mixture
- No evidence of other causative factors (recent HI, alcohol/drug intoxication, status epilepticus, AED toxicity)
Post Ictal Psychosis

- < 18% of patients with medically intractable focal epilepsy
- Gap between development of epilepsy and psychosis is (mean) 15-20 years
- Usually occurs after exacerbation of seizures (clusters)
- Lucid interval = 1-6 days (problem for family!!! – “calm before the storm”)

Shining a light on the future
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Post Ictal Psychosis: Risk Factors

• Usually after partial seizures (psychic aura – ictal fear)
• Bilateral TLE
• Early age of onset/long duration of epilepsy
• Low IQ
• PH of depression
Post-ictal Psychosis: Phenomenology

- Varies widely
- Onset – usually confusion – then:
  - Abnormal mood (> 2/3)
    - Usually depressed (90%), may alternate with hypomania
    - Irritable (70%)
    - May be suicidal (20%)
Post-ictal Psychosis: Phenomenology

- Delusional syndrome (90%)
- Often paranoid with prominent persecutory delusions
- Religious content is common
- May be grandiose
- Primary delusions/ thought disorder rare
Post-ictal Psychosis: Phenomenology

- Hallucinations (> 40%)
  - Auditory, visual or somatic
- 1/5 show aggressive behaviour – sudden unprovoked (often well-directed) violent attacks
- Patients tend to be fully orientated and MOST (not all) remember their psychotic episodes
- If patient has a generalised seizure while psychotic, the symptoms tend to deteriorate
Post Ictal Psychosis: Acute Treatment

- Most patients recover within 1 week regardless of medication
- Sedation (benzodiazepines) in supportive environment
- May need antipsychotics
Post Ictal Psychosis: Long-term Treatment

• Treat the epilepsy!!!!
  – Re-evaluate the diagnosis
  – Check compliance
  – Try 2\textsuperscript{nd} line anticonvulsants
  – Consider surgery

• Risperidone/clobazam for early symptoms eg insomnia

• Clobazam after a seizure to attempt to abort a cluster of seizures (10mg OD/BD for 2-3 days)
Post Ictal Psychosis: Prognosis

- PIP tends to recur (often in stereotyped way)
- Long-term antipsychotics – if frequent episodes
- 10-15% (Kanner < 40%) develop chronic inter-ictal psychosis
Chronic Interictal Psychosis
Schizophrenia-like Psychosis of Epilepsy - SLPE

- Psychosis lasting > 3 months
- 7-9% of people with epilepsy
- 1st described by Slater in 1963
- Tends to occur 10-15 years after the onset of epilepsy
Chronic Interictal Psychosis
Clinical Features

• Paranoid psychosis
• Religious delusions
• Preservation of affect and personality
• Lack of negative symptoms
• Psychosis may be “hidden”
  – ? risk greater than 9%
Risk factors for the development of SLPE

- Age of Onset of Epilepsy
  - Before/ around puberty
- Gender bias – female > male
- CPS > PGE (TLE most common)
- Frequent hospital admissions for epilepsy
- Post-ictal confusion
Mechanism for Development of Psychosis

- Psychosis may be a direct consequence of the epileptic discharge (Kindling)
  - Receptor-based changes and changes in cerebral blood flow
- On-going subictal activity in the limbic system undetectable on EEG
- Psychosis and epilepsy may have shared aetiology
  - Ventricular enlargement (MRI/post-mortem studies) in both CIP & schizophrenia
    - Neuronal migration disorder
Neuroimaging: MRI

- **Schizophrenia**
  - ↓ Whole brain volume, ↑ ventricles
  - ↓ volume of hippocampus + amygdala
- **Psychosis of Epilepsy**
  - ↓ Whole brain volume, ↑ ventricles
  - Tebartz van Elst *et al*, 2002 ep & psychosis cf TLE/normal
  - ↔ hippocampal volumes
  - ↑ amygdala volumes bilaterally
  - No difference between PIP and SLPE
Neurodevelopmental Disorder: Genetics

- Parental history (Mother > Father) of epilepsy is a risk factor for developing psychosis
- Parental history of psychosis is a risk factor for developing epilepsy
- Whether both epilepsy and psychosis may be different phenotypes of the same genotype
- Various chromosomes are suspected:
  - 16p13.11 heterozygous deletion
  - microdeletion in 15q 13-14 can result in schizophrenia or juvenile epilepsy
- Various genes are suspected eg LGI1 and genes encoding ion channels (eg: CACNA1C)
Chronic Interictal Psychosis
Treatment

• Neuroleptics in calm environment
• All neuroleptics reduce the seizure threshold – patients most at risk have cerebral damage
• Seizures are most likely to occur early in treatment or after a dose increment
• Avoid clozapine and chlopromazine (most epileptogenic)
• Avoid other pro-convulsant drugs
Chronic Interictal Psychosis Treatment

• No clear data re best antipsychotic to use (Farooq & Sherin, 2008)
• Try haloperidol, *risperidone*, olanzapine, quetiapine or aripiprazole
• Start with a low dose, gradually increase, monitor seizure frequency
• CBT
Epilepsy and Psychosis

Other Psychoses
Other Psychoses

• Drug Induced
• Depressive Psychosis
  – Mood congruent delusions
  – Treatment: antidepressant (sertraline), antipsychotic
  – ? ECT – omit morning AED

• Hypomania/mania
  – (rare in people with epilepsy ? Because already on mood stabilising AEDS)
Epilepsy and Schizophrenia

- **Bidirectional relationship**
- Increased risk of schizophrenia in people with epilepsy = $x \times 4.5 - 8.5$
- Increased risk of schizophrenia in people with history of febrile convulsions = 44%
- Increased risk of schizophrenia with parental history of epilepsy = $x \times 2$

- Increased risk of epilepsy in people with schizophrenia = $x \times 3$
- Increased risk of epilepsy in people with parental history of psychosis = $x \times 2.7$
Age at Psychosis onset

Schizophrenia

• Negative symptoms

• IF POSSIBLE – AVOID
• Clozapine – makes EEG worse and contraindicated with CBZ (WCC)
  – If necessary use/increase valproate esp at doses > 600mg)
• Depots
• Other pro-convulsant drugs
Epilepsy and Psychosis

Iatrogenic
• Medication/Surgery
Epilepsy and Psychosis Medication

- All AEDs have some psychiatric side effects
- Psychosis has been reported in < 12% (all AEDs are implicated – even if just single case reports)
- Worst culprits – ethosuximide, vigabatrin, topiramate, levetiracetam and zonisamide
- ?? Direct toxic effect of drug or forced normalisation
- Some AEDs are mood stabilising – mental state needs monitoring if they are withdrawn
Epilepsy and Psychosis Medication

- Mula *et al.*, (2007) – 108 patients had trials of TPM & LEV (different mechanisms of action)
- 1/3 had psychiatric adverse events
  - 5% just with LEV, 23% just with TOP
- 8% had psychiatric adverse events on both drugs
  - these patients had:
    - History of febrile convulsions
    - Past psychiatric history
    - Family psychiatric history
- 34% became seizure free
  - 27% became psychotic vs. 8% not seizure free (FN)
Acute Interictal Psychosis Forced Normalisation

- Brief psychotic episode (days to weeks)
- Paranoid delusions and auditory hallucinations
- More common when seizures have *suddenly* improved/ fully controlled (diagnosis - > 80% reduction in fit frequency in preceding month)
- AEDs, surgery, VNS
- Rare – 3/697 patients in one series
Forced Normalisation

• Episode of psychosis alternates with periods of increased seizure activity and may be terminated by a seizure
• Tends to be recurrent (even with other AEDs)
• May get premonitory symptoms of anxiety and insomnia (try anxiolytics)
Forced Normalisation: EEG

- (Landolt) – EEG normalised while psychotic – hence “forced” or “paradoxical” normalisation accompanying the “alternative psychosis”
- EEG does not always “normalise” but it tends to improve
- The EEG abnormalities return when the psychosis remits
- Remember in patients with definite epilepsy - 50% of single EEGs are normal anyway
Risks and Benefits of Surgery

• Many epilepsy surgery programmes exclude patients with a history of psychosis
• Concerns
  – Ability to undergo pre-op assessment/rehab
    • Reutens et al, 1997: no problems encountered
  – Ability to provide informed consent
  – ?? Post-op seizure freedom resulting in “forced normalisation”
  – Operation will not improve psychosis
Epilepsy Surgery and Psychosis Consent

• Capacity
  – 1) Understand information
  – 2) Retain the information
  – 3) Use or weigh up the information as part of the decision making process
  – 4) Communicate their decision
Epilepsy and Psychosis
Surgery: PIP: Kanner

- History of PIP predictive of bilateral ictal foci with 89% certainty
- So? Likely to have poor outcome with respect to seizure freedom
- And: higher risk of postsurgical mood disorder
- But: if seizure free – wouldn’t have PIP!
- History of PIP – more intensive search for bilateral foci
  - Longer telemetry
  - Depth electrodes
Epilepsy and Psychosis Surgery: CIP

- Marchetti *et al*, 2003: small series
  - All cooperated with investigations
  - All could give informed consent
  - In most: seizure outcome: Engel Class I
  - No post-op worsening of psychosis
  - Most improved psychiatrically
Post Operative De Novo Psychosis

- Psychosis may arise *de novo* following epilepsy surgery (1-7% - but ? would they have developed psychosis anyway??)
- Tends to occur within the 1st 6 months (and usually within 5 years)
- ? Pathological mechanism
- Occurs regardless of outcome of surgery with respect to seizures
- Psychosis is usually paranoid but may be depressive
- Tends to respond well to neuroleptics (risperidone)
Risk Factors for Post Operative Psychosis

- Bilateral EEG abnormalities
- ? Right-sided surgery (usually larger resection)
- Pre-operative anxiety
- Developmental lesions
Epilepsy and Psychosis
Is Surgery Contraindicated?

• No!
• Trimble (1992): “better to be psychotic without seizures than to be psychotic with them”
• Fenwick (1994): “Freedom from seizures is worthwhile despite unrelenting psychosis”
• Reutens (1997): No improvement in psychosis but improved Q of L – function and integrate better.
  – Less AEDs - less SEs and interactions.
  – May even be able to use clozapine.
Epilepsy and Psychosis: Summary

- Quite common (< 18% - PIP; < 9% SLPE)
- Latent period between onset of seizures and development of psychosis (15-20 years)
- Then, paranoid psychosis with auditory hallucinations – often religious theme
- **PIP** tends to occur after a **cluster** of fits
- Psychosis responds to neuroleptics
- Patients with epilepsy can develop other causes of psychosis!
Epilepsy and Psychosis: Questions

• ? Mechanism of development of psychosis
• ? Why latent period of 15-20 years between onset of epilepsy and development of psychosis
• ? Why lucid period before development of PIP after seizures
• ? Which antipsychotic to choose
• ? Role of CBT
Epilepsy and Psychosis: Referrals to Neuropsychiatry!

• Frequent (often daily seizures) – so cannot differentiate between peri-ictal and inter-ictal psychosis

• Severe epilepsy so are on several (<5) AEDs including topiramate and levetiracitem

• Often other complicating factors:
  – ABI from frequent seizures
  – “Self-treatment” with alcohol/illicit substances
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