Autism and co-occurring conditions: Epilepsy

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Questions to consider:

- How does epilepsy present in autistic people?
- Why do autism and epilepsy tend to co-occur?
- How is epilepsy managed in autistic people?
  - focusing on particular issues in managing epilepsy that come with also being autistic
- How could research help?
How does epilepsy present in autistic people?

- Prevalence of co-morbid epilepsy
  - In those with autism but not ID ~ 8% (meta-analysis by Amiet 2008)
    - compared to 1-2% in general population
  - Across all with autism - varies with sample ~ 6 – 27%
  - Increased risk
    - Autism + ID: if IQ<40 ~ 46%
      - compared to 35% across all with IQ<35
    - female sex: male : female (autism + epilepsy) ~ 2:1
      - (autism alone ~ 3.5:1)
      - treatment-resistant epilepsy also more common in females with autism than males.
  - age: peak of epilepsy onset is in adolescence
    - (in epilepsy alone = peaks in infancy and older adulthood)
How does epilepsy present in autistic people?

- Are some aspects of autism more common in those who also have epilepsy?
  - ~ early onset of autism, greater repetitive object use, unusual sensory interests, more motor coordination problems.
  - ? reflecting wider global developmental delay?

- Are some types of epilepsy more common in autistic people?
  - ~ both focal and primary generalised epilepsies occur.
How does epilepsy present in autistic people?

- Are there order effects?
  - Whilst peak age of epilepsy onset is later than age of autism diagnosis, epilepsy may precede or follow appearance of autistic aspects
    - Comorbidity may complicate / delay both diagnoses.
  - Epileptic encephalopathy (Landau-Kleffner syndrome) with subsequent autistic features (especially communication abilities) developing after age of three years
    - ? relationship between ‘features of autism’ and Autism?
Why do autism and epilepsy tend to co-occur?

- No evidence that autism causes epilepsy
- No evidence that epilepsy causes autism

- shared origins;
  - Tuberous sclerosis, Angelman, Fragile X, ...
  - Various candidate genes
Evidence of shared origins
– a population study (Christensen et al 2016)

– Cumulative incidence of epilepsy at 20 years of age = 1.63% if older sibling is NOT autistic.

– Cumulative incidence of epilepsy at 20 years of age = 2.54% - if older sibling is autistic,

– Cumulative incidence of autism at 20 years of age = 1.27% if the older sibling does NOT have epilepsy.

– Cumulative incidence of autism at 20 years of age = 2.06% - if older sibling has epilepsy,

– If older sibling has both autism + epilepsy, younger sibling also more likely to have both

> Suggests - shared causative genes and / or environment

> or - gene – environment interactions
Candidate genes and functions
(Torre-Ubieta et al 2016)

- **SHANK3** less neurone production, abnormal Glu synapses
- **MECP2** increased cell death, reduced dendritic spines and synapses
- **CACNAIC** neural progenitor cell proliferation, dysregulated Ca$^{2+}$ signalling

- Excitatory / Inhibitory imbalance
- Changes in cortical connectivity patterns
❖ How is epilepsy managed in autistic people?

- Diagnosis
- Epilepsy management plan
- Seizure rescue plan
- Choice of medication
- Seizure diary (tailored and clear)
- SUDEP risk assessment
How is epilepsy managed in autistic people?

- Epilepsy – the most common cause of premature death in those with autism & ID

- ? related to epilepsy itself, or an underlying disorder, or, problems in health monitoring (adverse effects, treatment adherence, challenges in seeking and obtaining appropriate healthcare)
What are the aims of epilepsy treatment?

- Associated co-morbidities
- AED side-effects
- Functional abilities
- Social & psychological
- Morbidity & mortality
- Severity & complexity of seizures
- QOL
Diagnosis

- Epilepsy is a clinical diagnosis
  - The complexities of seizure classification (ILAE 2017)
    - Current knowledge is insufficient to enable scientifically based classification
  - Focal seizures – have a localised focus
    - awareness is used as a classifier of focal seizures;
    - focal seizure types; automatisms, behaviour arrest, hyperkinetic, autonomic, cognitive, and emotional
  - Generalised seizures – EEG appears to show simultaneous onset across the cortex
    - Tonic clonic, absence, myoclonic absence, myoclonic-atonic, myoclonic-tonic-clonic
  - Focal or Generalised
    - atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset;
    - focal to bilateral tonic-clonic seizure (was secondarily generalized seizure)
  - Seizures of unknown onset
- Diagnosis - issues particularly related to autistic people with ID

- Is it a seizure?
  - Stereotypic self-stimulation,
  - repeated blinking or swallowing,
  - spontaneous smiling or grimacing,
  - periods of apparent psychomotor arrest,
  - dystonic posturing, stereotypic movements, mannerisms,
  - ataxia with falls,
  - non-epileptic paroxysmal behaviours - rage, agitation
  - NES.

- EEG video telemetry may help, but hard to tolerate
Epilepsy management plan

1. Clarify the clinical issues
   - History: seizure type(s), duration, severity, ? triggers, response to AEDs, side-effects, comorbidities
   - Investigations: EEG (n.b. spikes common in autistic children without epilepsy), MRI brain

2. Provide appropriate training
   - what is epilepsy, supporting a person in a seizure, keeping a diary, AEDs, rescue medication

3. Draw up the plan
   - Observations (diary), risk assess routines, AEDs

4. *Share plan with patient (if possible), all carers, GP
Share understanding of epilepsy with patient (if possible), carers and GP

- Ensure that carers understand the purpose and the limits of the plan
  - eg. Rescue treatment for emergency epilepsy management - not challenging behaviour
- If carers require support for other management / behavioural issues, address these independently
- Work through with carers to ensure clarity
- Review safety and efficacy of plan in action
Seizure rescue medication plan

- **Aim:** to terminate an extended seizure or series of seizures
  - For individuals with an established diagnosis of epilepsy
  - Not for the management of ‘normal’ seizures

**Associated aims** *(Duncan et al 1995):*
- Halt seizure activity rapidly
- Prevent injury
- Maintain cardiorespiratory function
- Avoid other secondary medical complications
Choice of epilepsy treatments

- No evidence (so far) that any AED is better or worse for epilepsy in the context of autism
- Use similar principles to managing epilepsy in the rest of the population;
  - Seizure type (focal, primary generalised) – Look at BNF
  - AED side effect profile; sedation, behavioural effects
    - ? additional benefit; mood stabilisation (Ltg)
  - Consider risks of drug interactions
  - Consider physical treatments; VNS, surgery
- Introduce AEDs carefully
- **WITHDRAW SLOWLY** – risk of seizure recurrence
Correlation of AED mechanism of action with clinical indication  (Patsalos 2013)

- AEDs with selective effects on voltage-gated Na+ channels (CBZ, OXC, PHT, ESL?)
  - Efficacy in:
    - Focal seizures
    - Generalised tonic-clonic seizures
  - No efficacy in:
    - Absence seizures
    - Infantile spasms
    - Lennox-Gastaut syndrome
    - Myoclonic seizures
- but currently mechanism-based approaches not that helpful
AEDs and psychiatric symptoms

- **Polytherapy**
  - *Increases risks of cognitive slowing and psychopathology*

- AEDs with highest risk of depressive symptoms in epilepsy are those acting at benzodiazepine-GABA receptor complex (includes barbiturates, topiramate and vigabatrin)
  - **Topiramate** - confusion, impaired concentration, depression, psychosis
  - **Tiagabine** - nervousness, depression, psychosis (? FN)
  - **Levetiracetam** - agitation, anxiety, depression, depersonalisation
  - **Lamotrigine** - confusion
  - **Oxcarbazepine** - drowsiness
  - **Pregabalin** - dizziness, drowsiness
  - **Valproate** – risks to foetal neurodevelopment
**Epilepsy treatments**

- If no improvement or seizure frequency increase;
  - Review diagnosis – ‘are these seizures?’

- Consider possible treatment errors
  - missed doses
  - excessive doses

- Consider other causes
  - eg. concurrent illness
  - pyrexia, metabolic disturbance (dehydration, acute hyponatraemia, acute renal / hepatic failure)
Additional epilepsy management challenges in autistic people

- May be multiple or hard-to-define seizure types
- Seizures may be overlooked
- Increased frequency of AED refractoriness
- Increased polypharmacy with increased side-effect risk
- Challenges communicating experience of adverse effects
- Challenges complying with monitoring requirements, eg. blood tests
Management of epilepsy in autistic people

- Additional observations
  - Utility of a baseline EEG in people with autism without epilepsy is doubtful
  - Whilst AEDs can have a positive impact on behaviour, no evidence that treatment of the epilepsy changes core aspects of autism; social, language, cognitive, behavioural aspects
SUDEP RISK SCREENING CHECKLIST

**Name:**
**DOB:**
**DATE:**

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>Mean Odds Ratio/Severity of risk</th>
<th>If present TICK, If not CROSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.42</td>
<td></td>
</tr>
<tr>
<td>Duration of epilepsy &gt;15 years</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>Age of onset of epilepsy &lt;16 years</td>
<td>1.85</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy with AEDs</td>
<td>2.50</td>
<td></td>
</tr>
<tr>
<td>1-2 GTSC per year</td>
<td>5.10</td>
<td></td>
</tr>
<tr>
<td>3 or more GTCS per year</td>
<td>15.56</td>
<td></td>
</tr>
<tr>
<td>50 or more seizures of any type per month in the last year</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>No GTSC and polytherapy</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>1-2 or unknown GTSC and no therapy/monotherapy</td>
<td>4.92</td>
<td></td>
</tr>
<tr>
<td>3 or more GTSC per year and no therapy/monotherapy</td>
<td>13.90</td>
<td></td>
</tr>
<tr>
<td>3 or more GTCS &amp; polypharmacy</td>
<td>25.20</td>
<td></td>
</tr>
<tr>
<td>Nocturnal seizures but NOT supervised and/or monitored during sleep</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Recent change of AED medication</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>NO staff training in SUDEP</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Drugs with potential cardiopulmonary risks</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>History of prolonged seizures, low pO2 or bradycardia during seizure</td>
<td>moderate</td>
<td></td>
</tr>
</tbody>
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**Notes**
- Static Risk factors
  - Male Gender
  - Presence of Learning Disability
  - Early onset of Epilepsy
  - Younger age
- Modifiable Risk Factors
  - High seizure frequency, especially GTCS
  - Number of concomitant AEDs
  - Lamotrigine and Carbamazepine associated with higher risk.
  - Treatment changes that are too quick carry higher risk.
  - Drugs with cardiopulmonary risks have more risk
  - Pre-existing cardiopulmonary impairment carries more risk
  - Prolonged seizures, marked cyanosis, bradycardia, apnoea increase risk
  - Supervision after seizures reduces risk
  - Monitoring and supervision at night reduces the risk.
  - Prone position may increase risk.
  - Non compliance with medication may increase risk.

**Based on**

**Key:**
- AED- Anti Epileptic Drugs
- GTSC- Generalised Tonic Clonic Seizure
- pO2 Oxygen saturation

**Overall Risk Rating:**

Collated by Chawira A. (2014)
Other possible consequences of comorbid epilepsy

- Additional psychopathology
  - Eg. ADHD, anxiety disorder, sleep disorders
- Increased strain on all concerned
- Additional social stigma and fear of epilepsy
  - Limitation of opportunity
  - Greater social isolation
How could research help understand the conjunction of epilepsy and autism?

- Is it valid to extrapolate results from the wider epilepsy research field to autistic people?
  - Is the epilepsy that occurs in autistic people sufficiently different from epilepsy in other populations to benefit from distinct and potentially novel treatment approaches?
- How does the nature and experience of having epilepsy and its treatments impact on everyday life for autistic people?
How could research help manage monitoring and risk?

- In the context of increased mortality rates of epilepsy in autism, can predictors of this risk be identified?
- How can we best, and most acceptably, educate people about the risks of Sudden Death in Epilepsy?
- Are wearable technologies that will be increasingly used to monitor epilepsy autism-friendly?
How could research help understand medication effects?

- Do psychotropic medications sometimes taken by autistic people alter manifestation or management of epilepsy?

- What effects might being autistic have on epilepsy treatments?
  - For instance, will AED behavioural side-effects vary?
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