Comorbidity in children with epilepsy

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What is comorbidity?

Comorbidity refers to a greater than coincidental presence of two disorders in the same person but it does not infer a causal relation.
Behaviour

Intellectual ability

Interictal discharges

Antiepileptic drugs

Seizure related factors

Psychosocial factors

Etiology / brain lesion

Behaviour
Comorbidities

Cognition?
Cognition in epilepsy

Berg et al 2008  *Connecticut study*  *Epilepsia* 2008  49:608

Assessment at 8-9 yrs

- Global cognitive dysfunction  73.6%
- Borderline  5.1%
- MMR (IQ60-69)  3.4%
- Mod-severe MR IQ<60  7.3%
- ‘Devastating’  4.7%
- Impaired NFC  5.9%
Neuropsychological status at seizure onset in children

Fasteneau et al Neurology 2009

• 282 children at or near onset epilepsy vs 147 healthy siblings
• 6-14 yrs, first seizure within three months, IQ>70
• 27.4% children vs 18.7% siblings psychological deficit
Cognition in newly diagnosed epilepsy

Jackson et al J Pediatr 2012

IGE (n=41) Cognitive z-scores

- Verbal IQ
- Performance IQ
- Reading
- Spelling
- Arithmetic
- Naming
- Expressive Vocab
- Picture Vocab
- Delayed Recall
- Immediate Recall
- Letter Fluency
- Category Switching
- Inhibition
- Correct Sorts
- CPT Inattention
- CPT Impulsivity
- Digit Symbol-Coding
- Grooved Peg Board

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Legend:
- IQ
- Academic Performance
- Language
- Memory
- Executive Function
- Motor
Intellectual development in children with & without epilepsy

*Muter, Taylor & Vargha Khadem 1997*
‘Epileptic Encephalopathy’

‘the epileptic activity itself contributes to cognitive and behavioral impairments beyond that expected from the underlying pathology alone (e.g. cortical malformation)’

Concept that can be applied to any individual where epileptic activity thought to contribute to cognitive impairment
‘West Syndrome’

– Infantile Spasms
– Hypsarrythmia
– Developmental plateau

85% developmental compromise, 60% ongoing seizures  
*Early treatment - improved outcome*
Benign Epilepsy with Centro Temporal Spikes

Not so benign?

- Language dysfunction despite typical course
  
  *Staden et al 1998*

- Cognitive deficits associated with prevalence of seizures & degree of EEG abnormality
  
  *Metz Lutz et al 1999*

- Impairment at onset during active phase – recovery of all but verbal short term memory
  
  *Metz-Lutz & Filipini 2006*

- Long term review specific language deficits
  
  *Monjauze et al 2011*
Dravets syndrome (Severe Myoclonic Epilepsy in Infancy)

• 1% of the epilepsy population

• Normal early development/imaging

• Febrile and afebrile general and unilateral prolonged clonic or tonic-clonic seizures in the 1st year of life (100%)

• Later appearance of myoclonus (80%), atypical absences (40%), focal seizures (46%)

• Developmental delay progressively apparent

• All seizure types resistant

• Interictal EEG: normal initially, generalized discharges

• Prognosis always unfavorable, for seizures, cognitive development, high mortality rates (up to 9%)

• Treatment with VPA, CLB, stiripentol, PB
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Cognitive outcome

Chiron, 2003; Wolf 2001
Wolff, Casse-Perrot & Dravet 2006

Severe myoclonic epilepsy of infancy
(Dravets syndrome)
Severe Myoclonic Epilepsy of Infancy

Treatment to avoid?

Lamotrigine and Seizure Aggravation in Severe Myoclonic Epilepsy

Renzo Guerrini, *Charlotte Dravet, *Pierre Genton, Anna Belmonte, †Anna Kaminska, and †Olivier Dulac

Institute of Child Neurology and Psychiatry, University of Pisa, Institute for Clinical Research Stella Maris Foundation, Calambrone, Pisa, Italy; *Centre Saint Paul, Marseille; and †Neuropédiatrie, Hôpital Saint-Vincent-de-Paul, Paris, France.

21 children, SMEI, 3 centres

>50% increase in convulsive seizures

Aggravation of myoclonic seizures

8

18
Comparison with Wolff’s study -1-
First evaluation
Comparison with Wolff’s study (2) – Follow up

Wolff et al

QD<40: 8/13

Personal series

QD<40: 4/16

Treatment was different

Nabbout et al, AES 2007
Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients

Francesca Ragona, *Tiziana Granata, †Bernardo Dalla Bernardina, ‡Francesca Offredi, †Francesca Darra, †Domenica Battaglia, *Monica Morbi, §Daniela Brazzo, ‡Simona Cappelletti, †Daniela Chiefo, *Ilaria De Giorgi, †Elena Fontana, *Elena Freri, **Carla Marini, ††Alessio Toraldo, †‡Nicola Specchio, §Pierangelo Veggiotti, †††Federico Vigevano, **Renzo Guerrini, ‡Francesco Guzzetta, and §§Charlotte Dravet

Epilepsia 2011 52:386-392

Figure 1.
Cognitive development of individual patients. Mean decrease of GQ is 33 points.
Epilepsia © ILAE

Figure 2.
Cognitive development of patients of group 1 (cases 1–19, Table 1), mean decrease of GQ is 39 points.
Epilepsia © ILAE

Figure 3.
Cognitive development of patients of group 2 (cases 20–26, Table 1), mean decrease of GQ is 12 points.
Epilepsia © ILAE
Dravet syndrome—epileptic encephalopathy?

Catarino et al Brain 2011 [eprint 29 June]

• 22 adult cases – oldest 60 years
• Neurological deterioration occurred throughout life
• 7 had drug changes following diagnosis
• 3 meaningful follow-up – 2 improvement in cognition, one spontaneous language
• PM no consistent cerebral structural changes, cell loss or neurodegeneration
Cognitive outcome in epilepsy

Early onset/ongoing seizures are associated with poor developmental outcome

Vasconcellos et al, 2001, 100 surgery candidates
Younger age onset associated with lower FSIQ score

Cormack et al 2005 79 children, temporal lobe resection
Age seizure onset predictive of IQ outcome
50 consecutive children
age 3-7 yrs
preoperative IQ<70 70%
85-115 16%

Postoperatively
6-12m: 41 (82%) showed stable developmental velocity; 3 gains >15, 3 not assessable to assessable
2-3 yrs: 29/40 stable developmental velocity, 8 gains >15
• Gains only seen where SF, ass with shorter duration epilepsy

Freitag & Tuxhorn
Developmental progress after early surgery

Cognitive outcome after temporal lobe surgery in childhood

42 <16 years, >5 year f/up
11 non surgery controls

Pre- and post-surgical IQ

- IQ increase* (>15 pts):
  Surgery group: 11 patients
  Control group: none

- IQ decreases* (>10 pts):
  Surgery group: 1 patient

* Criteria of Tuxhorn & Freitag (2005)

IQ range

Skirrow et al Neurology 2011;76:1330-1337
Cognitive outcome after temporal lobe surgery in childhood

IQ change across the post-op period

- Variability in IQ changes until 4-6 years post-op
- IQ improvements detectable >6 years post-op
Developmental progress after early surgery

Roulet –Perez et al Epilepsia 2010;51:1266-1276
Comorbidity

Behaviour?
Jo

- Age 6 years
- First seizure age 3 years;
  - GTC seizure; further seizure after 2 weeks
- Commenced on sodium valproate
- Myoclonic jerks, atonic attacks, nonconvulsive status
- Poor focus, constantly on the go
- Addition of clobazam
- Angry, aggressive, erratic,
- Levetiracetam introduced, clobazam withdrawn, continued seizures
- Poor concentration in school, ?switching off
- Flitting from activity to activity

What is the likely cause of his behaviour difficulties?
Behaviour & epilepsy

• Likely to be multifactorial in origin
  – *Frequent seizures, NCS, intellectual disability, medication*
• Caring neurologist likely to be presented with behaviour as one of the most troubling aspects of management
• Child mental health services limited
• Assessment remains multidisciplinary, and often requires careful evaluation and discussion amongst all professionals involved
Mental health problems in epilepsy

IOW – 1970

• 7% general population
• 12% disorders not involving CNS
• 28% idiopathic seizures
• 38% structural brain abnormality
• 58% seizures + structural brain abnormality
Psychiatric disorder in epilepsy  
**N=10438, age 5-15 years**  
*British Child and Adolescent Mental Health Survey*

<table>
<thead>
<tr>
<th>Group</th>
<th>% with psychiatric disorder</th>
<th>% SLD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any (N)</td>
<td>Emot</td>
</tr>
<tr>
<td>Epilepsy plus (25)</td>
<td>56.0% (14)</td>
<td>16.0% (4)</td>
</tr>
<tr>
<td>Pure epilepsy (42)</td>
<td>26.2% (11)</td>
<td>16.7% (7)</td>
</tr>
<tr>
<td>Diabetes (47)</td>
<td>10.6% (5)</td>
<td>6.4% (3)</td>
</tr>
<tr>
<td>All other (10,202)</td>
<td>9.3% (946)</td>
<td>4.2% (427)</td>
</tr>
</tbody>
</table>

Any, any psychiatric disorder, not including learning disability; Emot, any emotional disorder; Cond, any conduct disorder, including oppositional defiant disorder; ADHD, any attention deficit/hyperactivity disorder; PDD, any pervasive developmental disorder (autistic disorder); SLD, severe learning disability

Is There A Problem?

% where parents think there is a definite or severe problem (SE)

Davies, Heyman & Goodman 2003
Behavioral and Intellectual Ability: A Complex Interplay

**Antiepileptic Drugs**

**Seizure Related Factors**

**Psychosocial Factors**

**Interictal Discharges**

**Etiology / Brain Lesion**

**Behavior**

**Psychosocial Factors**
Role of epilepsy

• Individual seizures
  – Prodromal
  – Ictal
  – Postictal

• Seizure control
  – Recurrent frequent seizures
  – Recurrent status epilepticus

• Subclinical discharges
Effect of suppression of ID on behaviour

*Pressler et al J Peds 2005;146:112-117*

**Bar Chart**

- **Patients with reduction of ID**
- **Patients without reduction of ID**

- **Antisocial**
- **Anxious/shy**
- **Conduct disorder**
- **Hyperactive/immature**
- **Learning problem**
- **Obsessive compulsive**
- **Psychosomatic**
- **Restless/disorganized**

**Legend**

- Improvement of Behaviour
- Deterioration

**Statistical Significance**

- *p<0.05
Role of underlying pathology

Davies et al *Dev Med Child Neurol* 2003:45:292-295

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any</th>
<th>Emot</th>
<th>Cond</th>
<th>ADHD</th>
<th>PDD</th>
<th>SLD</th>
</tr>
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<tr>
<td>Epilepsy plus (25)</td>
<td>56.0% (14)</td>
<td>16.0% (4)</td>
<td>24.0% (6)</td>
<td>12% (3)</td>
<td>16% (4)</td>
<td>35.0% (7/20)</td>
</tr>
<tr>
<td>Pure epilepsy (42)</td>
<td>26.2% (11)</td>
<td>16.4% (7)</td>
<td>16.7% (7)</td>
<td>0</td>
<td>0</td>
<td>2.4% (1/41)</td>
</tr>
</tbody>
</table>

Higher rates of behaviour disorder (and SLD) in children with epilepsy associated with other problems, ie more likely to have underlying pathology
Temporal lobe epilepsy
Psychiatric comorbidity

No of Children (%)
Pre-operative
Post-operative

Psychiatric diagnosis (DSM-IV)

PDD
ADHD
ODD/CD
DBD
Emotional disorder
Eating disorder
Conversion disorder
Psychosis
Psychiatric outcome in extratemporal epilepsy  \( N=71 \)

Colonelli et al Dev Med Child Neurol 2012;54:521-526

<table>
<thead>
<tr>
<th>Male : Female</th>
<th>38 (53.5%) : 33 (46.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right : Left lesion side</td>
<td>35 (49.3%) : 36 (50.7%)</td>
</tr>
<tr>
<td>Lesion Site</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>52 (73.2%)</td>
</tr>
<tr>
<td>Parietal</td>
<td>12 (16.9%)</td>
</tr>
<tr>
<td>Occipital</td>
<td>7  (9.9%)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>FCD</td>
<td>34 (47.9 %)</td>
</tr>
<tr>
<td>Tumour</td>
<td>17  (23.9%)</td>
</tr>
<tr>
<td>TSC</td>
<td>7    (9.9%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>2    (2.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>11   (15.5%)</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>52  (73.2%)</td>
</tr>
<tr>
<td>Neurological dis.</td>
<td>12  (16.9%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7   (9.9%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>5    (7%)</td>
</tr>
<tr>
<td>Neurological and Psychiatric disorders</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

Psychiatric disorders pre- and post-operatively

Fig. 56.3 54.9

<table>
<thead>
<tr>
<th>Pre-operatively Psychiatric Diagnoses</th>
<th>Post-operatively Psychiatric diagnoses</th>
</tr>
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<tbody>
<tr>
<td>43.7</td>
<td>45.1</td>
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</table>
Predisposition

Children have higher rate of behaviour problems prior to first seizure

Austin et al *Pediatrics* 2001;107:115-122
116 girls, 108 boys, mean age 8.4 vs 135 siblings mean age 9.9
Recruited within 6 weeks first recognised seizures, CBCL
Higher rates of behaviour problems in 6m prior to first recognised seizure; higher total internalising, attention, thought, and somatic complaint scores than siblings

Hesdorffer et al *Arch Gen Psychiatry* 2004 ;61:731-736
109 children, 218 controls mean age 9.2 years
Interview schedule for DSM-IV
ADHD 2.5x more common in children with newly diagnosed seizures; predominantly inattentive rather than hyperactive impulsive type, or combined.
Role of AEDs

• Administered at onset of epilepsy
• Always impossible in an individual to tease out effect of medication vs effect of seizures
• Perception of administering CNS drug – *inevitable* affect on behaviour
Problems with studies

• Newly diagnosed vs poorly controlled
• Healthy volunteers not the same as individuals with epilepsy!
• No correction for effects of seizures
• Wide range of different types of epilepsy lumped together
• Comedication, drug dosage, levels (?toxicity) not taken into consideration
Reported AED effect on cognitive function and mood

<table>
<thead>
<tr>
<th>Motor and cognitive speed</th>
<th>Memory</th>
<th>Mood</th>
<th>Psychosis</th>
</tr>
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<tbody>
<tr>
<td>Phenobarbital</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>−</td>
<td>−</td>
<td>+*/↔</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>−</td>
<td>−</td>
<td>−/↔</td>
</tr>
<tr>
<td>Valproate</td>
<td>−</td>
<td>−</td>
<td>+*/↔</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>↔</td>
<td>↔</td>
<td>−</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>↔</td>
<td>↔</td>
<td>+*/↔</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>↔</td>
<td>↔</td>
<td>−</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↔</td>
<td>↔</td>
<td>+*/↔</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>↔</td>
<td>↔</td>
<td>−</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>−/↔</td>
<td>↔</td>
<td>+*/↔</td>
</tr>
<tr>
<td>Topiramate</td>
<td>−/↔</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>−/↔</td>
<td>−</td>
<td>−</td>
</tr>
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</table>

Data from Mula and Monaco, unless otherwise stated. − = negative effect. + = positive effect. ↔ = no effect. * Data from psychiatry published work.

Table 5: Cognitive and psychotrophic effects of seizure drugs

Taken from Lin, Mula & Hermann Lancet 2012;380:1180-1192
Possible intervention

• Review of seizure control
• Review of AEDs
• What are the main triggers to behaviour?
• Consideration of modification of behaviour
• Medication
  – ? true risk of seizures with stimulant medication
Review of seizure control

• Has there been a change in seizure type, severity or frequency?
• Are there significant EEG changes without related seizures?
• Is the behaviour peri-ictal?
• Has there been medication change; could it be the AED or has seizure control caused an ‘awakening’
Review of behaviour

• Are there any triggers to behaviours?
• Is it persistent or intermittent?
• Is the behaviour situational?
• Has anything worked in modifying the behaviour?
• Is the child’s cognitive level known?
  – Does the child have specific learning difficulties?
• Has the family appropriate support?
• Have teachers/carers realistic expectations?

?role for behaviour modification

?role for medication
The child with epilepsy

Medical
- Seizure frequency
- Medication load

Psychosocial
- Peer relationships
- Education
- Epilepsy syndrome
- Cognition
- Behaviour
- Expectations
- Family impact
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