Current views on epilepsy management

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UCL-Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London & Young Epilepsy, Lingfield, UK
What are our current challenges?

• Optimising diagnosis

• Optimising treatment
  — What is our evidence base?
  — availability
  — Compliance
  — Ease of maintenance
  — expense

• Optimising services
What have we got to guide us?

• 60,000 UK children
• Continuing concerns regarding quality of epilepsy care and misdiagnosis
Goals of management

• Accurate diagnosis
• Prompt and optimal investigation
• Accurate diagnostic & prognostic information for families
• Seizure freedom
• No adverse effects to treatment
• Ease and optimal timing of referral for complex patients
Needs of families

• Accurate diagnosis
• Access to information
  – Need for ongoing discussion
• Access to expertise
• Access to change of treatment
• Access to multiagency working
Diagnosis by specialist
With investigations as necessary:

- Uncertain
- Epilepsy
- Non epileptic attack disorder

Further investigation including assessment of other physical causes (e.g. Cardiac) or Referral to tertiary care

Investigation and classification by seizure type and epilepsy syndrome by specialist

Treatment

Referral to tertiary care

NICE

Referral to psychological or psychiatric services
Suspected seizure

Primary care

Information obtained about the event
Physical examination

A&E
(protocols in place for assessment)
Initial screening by paediatrician

Diagnostic
Doubt

Suspected non-febrile seizure

Treatment with AEDs only in exceptional Circumstances:

Referral to specialist as soon as possible
(The GDG recommended within 2 weeks)

Referral to epilepsy specialist or Other Specialist (eg. cardiologist)

NICE 2004
Referral to Tertiary Care

- Behavioural or developmental regression
- Unidentifiable epilepsy syndrome
- <2yrs of age
- Seizures not controlled within 2 yrs
- 2 AEDs have been unsuccessful
- Unacceptable medication side effects
- Unilateral structural lesion
- Psychiatric co-morbidity
- Diagnostic doubt

NICE 2004
Access to services

• Paediatrician ‘with an expertise’
• Clinical nurse specialist in epilepsy
• Paediatric neurologist
  – 90 WTE in UK
• Child & adolescent mental health services
Service Descriptors

- Units with Epilepsy Specialist Nurse(s):
  - With: 102, Without: 91
  - Percentage: 53%

- Units with Paediatric Neurology Clinic(s):
  - With: 164, Without: 29
  - Percentage: 85%

- Units with 'Epilepsy Clinic(s)'
  - With: 112, Without: 81
  - Percentage: 58%

- Units with Young People's clinic:
  - With: 35, Without: 158
  - Percentage: 18%

Legend:
- Green: With
- Red: Without
Paediatrician with expertise in epilepsies
- Performance indicator score (%): 79
Epilepsy Specialist Nurse
- Performance indicator score (%): 46
Paediatric Neurologist
- Performance indicator score (%): 60
Appropriate first clinical assessment
- Performance indicator score (%): 65
Seizure classification
- Performance indicator score (%): 87
Syndrome classification
- Performance indicator score (%): 37
ECG
- Performance indicator score (%): 40
EEG
- Performance indicator score (%): 92
MRI
- Performance indicator score (%): 64
Carbamazepine
- Performance indicator score (%): 95
Withdrawal of diagnosis
- Performance indicator score (%): 89
Pregnancy or contraception discussion
- Performance indicator score (%): 38
“All children with epilepsy under 2; or with 3 or more epilepsy drugs should have input from a paediatric neurologist”

UK = 245/407 = 60%
Seizure - An evidence based guideline for the management of children presenting post seizure

Authors: Dr Kate Armon, Dr Marie Atkinson, Miss Philippa Ecclesathan, Dr Monica Lathropaul, Dr Roderick MacFaul, Dr Stephanie Smith, Dr Ursula Wermke, Dr William Whitehouse, Dr Lynne Williams, Professor Terence Stephenson

Publications: Children Nationwide Date: January 1998 Updated July 2002

Guideline

Care Pathway

THE CHILD WITH A SEIZURE
Evaluate and maintain ABC.
If still seizing - follow status policy 4.3
Please tick box when completed. Circle Y / N
If deviations from pathway occur please record in variance table (page 3)
Complete Nursing, History and Examination for all. Then complete Box A or B or C as applies.

DATE...........

NURSING assessment: Nurse name: ...................... Triage score: .............. Position with Oxygen and suction ☐

BM ☐ Result: .............. Antipyretics given ☐
Freq. of obs ☐
Required: .............. NB Only rgt BP: Sats if abnormal

Other comments: ........................................

MEDICAL assessment: Print name (Dr): ........................................ Time ..............

HISTORY: History taken from: ........................................ eye witness Y / N Child’s age: ..............

HPC: ........................................

Time of start of seizure: .............. Duration: .............. mins

Description: ........................................ Any focal features Y / N Multiple in 24 hours Y / N If yes, number and duration: ..............

History of other symptoms (fever etc): ........................................

EXAMINATION

General appearance: ........................................

CVS RS ABD

NEURO

BP ..............

OFC
## 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</td>
<td>Emot</td>
</tr>
<tr>
<td>Epilepsy plus (25)</td>
<td>56.0%</td>
<td>16.0% (4)</td>
</tr>
<tr>
<td>Pure epilepsy (42)</td>
<td>26.2%</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%</td>
<td>4.2%</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

Transition of care

considerations in management

• Medical
  – Who is likely to be the responsible physician - GP, neurology, psychiatry, learning disability?

• Psychosocial
  – Are they likely to be independent
  – What is the likely care environment
    
      To what degree will there be support from community based teams

• Education

*†Anne T. Berg, ‡Samuel F. Berkovic, §Martin J. Brodie, ¶Jeffrey Buchhalter, #**J. Helen Cross, ††Walter van Emde Boas, ‡‡Jerome Engel, §§Jacqueline French, ¶¶Tracy A. Glauser, ##Gary W. Mathern, ###Solomon L. Moshé, †Douglas Nordli, †††Perrine Plouin, and ‡Ingrid E. Scheffer
Reading Epilepsy

10 years

Childhood Absence

Adolescence Absence

2 years

Benign Myoclonic

Juvenile Myoclonic

1 month

Neonatal Convulsions

Myoclonic Absences

Rolandic

Occipital

Landau–Kleffner

C.S.W.S.

FOCAL LESIONAL or MRI-NEGATIVE

Partialis Continua Rasmussen

Progressive Myoclonic

OHTAHARA

West

Lennox–Gastaut

www.ILAE-epilepsy.org
Genetic

Concept: the epilepsy is the direct result of a known or inferred genetic defect(s). Seizures are the core symptom of the disorder.

Evidence: Specific molecular genetic studies (well replicated) or evidence from appropriately designed family studies.

Genetic does not exclude the possibility of environmental factors contributing
Structural-Metabolic

• **Concept:** There is a *distinct other structural or metabolic condition or disease* present.
  – eg. Tuberous sclerosis

• **Evidence:** Must have demonstrated a substantially increased risk of developing epilepsy in association with the condition.
Unknown

- **Concept**: The nature of the underlying cause is as yet unknown.
Report of the Commission on Classification and Terminology


New concepts proposed for classification of the epilepsies (brief version). *Epilepsia*, 2011

Quick Overview of the 2010 proposal for organization of the epilepsies

This 2-page document has been devised to be used as a clinical tool when seeing patients to facilitate use of the new organization in clinical practice.

http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfoverview.cfm
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

**Classification of Seizures**

**Generalized seizures**
- Arising within and rapidly engaging bilaterally distributed networks
  - Tonic-Clonic
  - Absence
  - Clonic
  - Tonic
  - Atonic
  - Typical
  - Atypical
  - Absence with special features
    - Myoclonic absence
    - Eyelid Myoclonia

**Focal seizures**
- Originating within networks limited to one hemisphere
  - Characterized according to one or more features:
    - Aura
    - Motor
    - Autonomic
    - Awareness/Responsiveness: altered (dyscognitive) or retained
  - May evolve to
  - Bilateral convulsive seizure

**Unknown**
- Insufficient evidence to characterize as focal, generalized or both
  - Epileptic Spasms
  - Other

**Changes in terminology and concepts**

<table>
<thead>
<tr>
<th>New Term and Concept</th>
<th>Examples</th>
<th>Old Term and Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic:</td>
<td>Channelopathies, Glut1 deficiency, etc.</td>
<td>Idiopathic: presumed genetic</td>
</tr>
<tr>
<td>Structure-metabolic:</td>
<td>Tuberous sclerosis, cortical malformations, etc.</td>
<td>Symptomatic: secondary to a known or presumed disorder of the brain</td>
</tr>
<tr>
<td>Unknown:</td>
<td></td>
<td>Cryptogenic: presumed symptomatic</td>
</tr>
<tr>
<td><strong>Terminology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-limited:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacoresponsive:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal seizures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolving to a bilateral convulsive seizure: eg. tonic, clonic, tonic-clonic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**References**
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

Electroclinical syndromes

One example of how syndromes can be organized:
Arranged by typical age at onset*

Neonatal period
- Benign neonatal seizures
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures*, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFIE)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures*, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)*
- Landau-Kleffner syndrome (LKS)

Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

Distinctive constellations/surgical syndromes

Distinctive constellations/Surgical syndromes
- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

Nonsyndromic epilepsies**

Epilepsies attributed to and organized by structural-metabolic causes
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- Tumor, infection, trauma, angioma, antenatal and perinatal insults, stroke, etc

Epilepsies of unknown cause

* The arrangement of electroclinical syndromes does not reflect etiology,
^ Not traditionally diagnosed as epilepsy
+ Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESES)
** Forms of epilepsies not meeting criteria for specific syndromes or constellations

This Proposal is a work in progress.....
We welcome your thoughts on this proposal. Please visit our Classification Discussion Group at: http://community.ilae-epilepsy.org/home/ to login and register your comments.
Dravet Syndrome

- Previously normal infant has seizures from ~ 6 mths
  - Hemiclonic or generalized seizures
  - Status, often with fever
  - Frequent convulsive seizures over next 6 mths

- Other seizure types by 1-4 years
  - myoclonus - usually by 4 years, not all patients
  - partial seizures, atonic seizures, atypical absences
  - hyperthermia common precipitant (bathing, fever)

Dravet syndrome

- Normal early development
- Slowing and regression after 1 year
- Ataxia and pyramidal signs often evolve
- EEG normal in first year, photosensitivity
- Generalized spike wave on EEG by ~ 2 years
- MRI normal

- Intellectual outcome poor, seizures refractory

SCN1A, sodium channel α1 subunit

- 70-80% Dravet children have mutations
- 95% de novo
- 10% cases -ve on sequencing have exonic deletion
Dravet Syndrome

STP – Placebo controlled trial

STICLO France

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Stiripentol</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>5%</td>
<td>71%</td>
<td>&lt;0.00002</td>
</tr>
<tr>
<td>Change seizure frequency</td>
<td>+ 7%</td>
<td>-70%</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Seizure free</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Dravet syndrome
*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 †Neuropédriatrie, Hôpital Saint-Vincent-de-Paul, Paris, France.

21 children, SMEI, 3 centres

>50% increase in convulsive seizures 8

Aggravation of myoclonic seizures 18
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 Chieffo, ¶Ilaria De Giorgi, †Elena Fontana, *Elena Freri, **Carla Marini, ††Alessio Toraldo, †††Nicola Specchio, §§Pierangelo Veggiotti, †††Federico Vigevano, **Renzo Guerrini, ¶Francesco Guzzetta, and §§Charlotte Dravet

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
Treatment – what are the challenges?

**Treatment**

- First line treatment AED after at least two epileptic seizures
- 66% respond to medication or enter spontaneous remission long term
- After failure of initial drug, 11% become seizure free

**Problems**

- No single treatment
- Choice of AED on individual basis
  - ‘best option’ AED
  - ‘do no harm’
- Many AEDs discovered by chance
- Often concern re side effects
- Data available from limited trials including few children
The ideal anticonvulsant

- Effective on multiple seizure types
- No exacerbation of other seizure types
- No side affects
- Predictable pharmacokinetics
- No interaction with other AEDs

Not there yet!
‘Older’ drugs

• Phenobarbitone
• Phenytoin
• Carbamazepine
• Sodium Valproate
• *Ethosuximide*

‘Newer’ AEDs

• *Lamotrigine*
• *Topiramate*
• *Oxcarbazepine*
• *Tiagabine*
• Levetiracetam
• Stiripentol
• Zonisamide
• Rufinamide
• Lacosamide
• Eslicarbazepine
• Retagabine
• Perampanel
## Newer AEDs

**Do they have advantages?**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater efficacy than other drugs in refractory epilepsy</td>
<td>Availability</td>
</tr>
<tr>
<td><em>Ability to prevent or delay onset of epilepsy</em></td>
<td>Expense</td>
</tr>
<tr>
<td>Broad usefulness in non epileptic CNS disorders</td>
<td>Long term review not available</td>
</tr>
<tr>
<td>Fewer adverse effects than available drugs</td>
<td>?safety</td>
</tr>
<tr>
<td>Ease of use</td>
<td>?efficacy over and above older drugs</td>
</tr>
<tr>
<td>Linear pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Lack of drug interactions</td>
<td></td>
</tr>
<tr>
<td>Longer half life</td>
<td></td>
</tr>
</tbody>
</table>
Generalised tonic clonic seizures

- Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed GTC seizures.
- Offer lamotrigine if sodium valproate is unsuitable. If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures.

Focal onset seizures

- Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures.
- Levetiracetam is not cost effective at June 2011 unit costs. Offer levetiracetam, oxcarbazepine or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value) if carbamazepine and lamotrigine are unsuitable or not tolerated.
Do we make a difference?

Pujar et al. Epilepsy Research 2010
Seizure freedom with additional drugs?

285 drug additions in 155 patients; 16% resulted in seizure freedom (28% SF)

What if the drugs don’t work?

• Reassessment of diagnosis
• Role of newer drugs
• Ketogenic diet
• Consideration for surgery
  – Resective surgery
  – VNS
The ketogenic diet

A high fat diet, designed to mimic the metabolic effects of starvation, used in the treatment of epilepsy.

Resource intensive; diet requires calculation.

Integrated service between paediatric neurologist & dietician with CNS input

As effective as any newer AED

*Not a natural treatment*
Alternative diets?

**Atkins diet**
- High fat low carbohydrate diet
  - 20g CHO/day
- No amount restriction – aim to eat to satiety
- No protein restriction – free foods are high protein foods

**Low GI diet**
‘Glycaemic Index’
Calculated from incremental area under blood glc curve after feeding indexed to ingested glc

Still require intense monitoring with input from dietician and knowledgeable medical team
Dietary therapy of epilepsy

Ketosis

KD 3:1
KD 4:1
MCT
MAD
LGIT

Infant | Pre-school | School age | Adolescent | Adult
Epilepsy surgery

- Removing source of seizures without further functional compromise to child
- Requires high resource multidisciplinary specialist assessment
- Early referral imperative to maximise outcomes
- Seizure freedom in 60-80% (cf 10% in drug resistant population)
Proposed criteria for referral and evaluation of children for epilepsy surgery

- ‘Paediatric Specialist Epilepsy Unit’
- No minimal expertise/infrastructure requirements
- Certain subgroups should be referred to unit with experienced multidisciplinary personnel, access to advanced technologies
  - Infants and toddlers
  - Hemispherectomy
  - Multilobar resection

Cross et al 2006
Epilepsia 2006;47:952-959
Who should be referred for assessment?

Catastrophic early onset epilepsy with evidence lateralisation

All children <24m, ?<5 with evidence focality, +/- MRI evident lesion

All children with evident focal epilepsy, or lateralised seizures associated with congenital hemiplegia resistant to two appropriate drugs

Specific syndromes require special consideration eg Sturge Weber, Tuberous Sclerosis, benign tumours associated with developmental regression +/- continued seizures
Vagal nerve stimulation

• Not curative
• *Selection of candidates?*
• Alleviation of seizures
  – Seizure duration
  – QOL
  – Seizure termination
• Access to services
Ways forward (1)

• Determining & locating individuals affected
• Ensuring care pathways and routes of referral in place
  – First seizure/new diagnosis
  – Ongoing review
  – Access to specialist services
• Managed clinical networks
• Identification & funding of regional specialist epilepsy services
Ways forward (2)

• Improving diagnostic accuracy
  – Imaging
  – Genetics

• Tailored treatment

• Prediction of response

• Optimal timing of alternative treatments