Treating NOE: The Perspective From a Longitudinal Study

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Disclosure

None
Learning Objectives

• Create awareness around the opportunity to study (“observe”) epilepsy at an early stage and to arrive at an appropriate individualized treatment decision

• Recognize the value of a longitudinal prospective approach (First Seizure Clinic) to better understand individual and collective treatment response
Treating New-onset Epilepsy

The Perspective of a Longitudinal Study

- Illustrative Case
- The Why
- Terms are critical
- Preliminary results
- Conclusions
Illustrative case

42 y/o M

- First generalized-tonic seizure 05_2009 with preceding subtle staring for few seconds only
- 2 weeks later referral and first evaluation at Halifax First Seizure Clinic
- Evidence for a prolonged complex-partial seizure in 04_2009, questionable SPS preceding
- Social Hx: Accountant, married, 2 children
- Family Hx: Paternal uncle epilepsy
- Neuroexam N; EEG left temp SW; MRI demo
Illustrative case

42 y/o M

- Dg: New-onset epilepsy
  Periventricular Heterotopia
- Treatment initiated
  LEV BID 750mg

MRI demo T2_FSE

Periventricular Heterotopia
Treating New-onset Epilepsy

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The Why

The Perspective of a Longitudinal Study in Treating NOE

Most of our knowledge about treatment response originates from retrospective cross-sectional studies and potentially has led to misperceptions & misconceptions.

The initial choice of AED in NOE is crucial: Monitoring the individual treatment course will allow new insights in individual time pattern and scenarios of pharmacoresistance.

Individual analysis is as important as group data.

Pohlmann-Eden B. Conceptual Relevance of New-onset Epilepsy. Epilepsia 2011, 52 (Suppl. 4):1–6
Etiology and Responder Rate

Symptomatic focal 35
Poststroke 54
Vascular malformation 45
Tumour 46
MRI neg 36
posttraumatic 30
Dysplasia 24
Hippocampal sclerosis 11
Dual Pathology 3

Semah et al. Neurology 1998;51:1256-1262

% seizure free patients > 1a

Paris N=2200
The unknown journey from A to B

Clinical Epileptogenesis

- Impact of syndrome-inherent factors
- Impact of seizure activity
- Impact of therapy
- Impact of genetics
- Impact of interplay of all these factors

First Sz  second Sz  Chronic Epilepsy

Tissue changes over time
Clinical Epileptogenesis

Opportunities
Longitudinal approach

- Risk factors for seizure recurrence after 1\textsuperscript{st} seizure (etiology / EEG)
- Analyze development of pharmacoresistance in the concert of treatment intervention and structural and functional data
Research is integral part

Genetics

MRI

EEG

Psychiatric Comorbidity

Cognition

Social issues

Function

Structure

Pathology
Damaged hippocampus in chronic epilepsy

A

First Seizure

Second Seizure

B

Chronic Epilepsy
Halifax MRI study after FS

Recruitment
Eligibility?
Hx & Px
EEG

First scan (T=0)
Hippocampal structure
Hippocampal volume
Structural lesions
MR spectroscopy
Diffusion tensor imaging

2nd scan (T=12 mo)
Hippocampal structure
Hippocampal volume
Structural lesions
MR spectroscopy
Diffusion tensor imaging

Follow-up (T=18 mo)
Pharmacoresistance?
NAA (or NAA/Cr) as a predictor of PR
Multifactorial predictive model for PR

Pohlmann-Eden, Crocker, Schmidt: Epilepsia. 2013, 54 Suppl 2:75–9
Treating New-onset Epilepsy

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Terms are critical

Epilepsy = “2 unprovoked seizures”?

Not clarified role of time interval between the 2 events

Interval 3 to 5 years

Interval > 10 years

Epilepsy?
Diagnosis of Epilepsy after one seizure only?

“…..a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure”

* Fisher et al. 2005: Epileptic Seizures and Epilepsy: Definitions proposed by the International League against Epilepsy (ILAE) and the International Buero For Epilepsy (IBE). Epilepsia 46: 470-472
Terms are critical

New-onset Epilepsy ≠ Newly diagnosed Epilepsy
“First Seizure” is often the first GTCS in presence of preceding subtle simple partial seizures

Critical role of distinguishing epileptic deja-vue from non-epileptic deja-vue

“First seizure” patients often have New-onset epilepsy or Newly Diagnosed Epilepsy

Subjective evidence

First SZ

10 20 30 40 years

= Cluster of simple partial seizures

Pohlmann-Eden AES 2013
"...the measures have different numerators. For new onset epilepsy, the numerator includes people identified at their second unprovoked seizure. In contrast, the numerator for newly diagnosed epilepsy (NDE) includes both new onset epilepsy and people with more than two unprovoked seizures who are first diagnosed with epilepsy during the study period..."
NOE defined as early stage of epilepsy

**NOE**  New-onset of epilepsy with evidence for $\geq 2$ seizures within $< 1^{\text{st}}$ year
(this includes frequent preceding simple or complex partial seizures)

**NDE**  Newly diagnosed epilepsy with evidence of ongoing seizures for $>> 1$ year.

**Time domain**  suggested in the definitions of NOE and NDE, rather than the absolute number of seizures, which often is hard to assess

Scenarios of newly diagnosed epileptic seizures
FIRST SEIZURE (FS), NOE and NDE
Treating New-onset Epilepsy

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“First Seizure” Presentations Nova Scotia

Halifax First Seizure Clinic  HFSC

Epidemiology:  Incidence of First Seizures (FS)  
General Population  40 – 70 / 100,000  per year

400 – 700 NEW FS-cases per year  
in a population of 950,000 in Nova Scotia

Referral Network FS - HFSC  
100-120 New Referrals per year
Recruitment of subjects:

- Ascertainment source: First Seizure Clinic (FSC) Queen Elizabeth II Health Science Center, Halifax, Canada (monocentric)
- Referrals from ER, hospital admissions, outpatient clinics, GPs, specialists
- Daily triaging of referrals (BPE, KL)
- Standardized database (>100 items)
- Multimodal assessment
- Prospective cohort
- Follow-up 6, 12, 24, 48 mth

Bernd Pohlmann-Eden (MD)
Karen Legg (NP)
Candice Crocker (Res Assoc)
Main Criteria for AED choice

- Syndrome (focal/ generalized)
- Efficacy
- Safety profile
- Tolerability
- Low interaction profile
- Speed of action
- Age / gender
- Comorbidities
- Special issues (weight, cognition)
- Drug cost / coverage
Drug of choice should have long-term safety, good tolerability, high seizure freedom rate, low interaction potential, allow good quality of life

*Note: New AEDs seem to fulfill this profile better*

This is specifically important for patients with New-onset epilepsy as *most patients might stay on the first AED for a long-time*

Always "individualized and tailored" Usually after 2 or more unprovoked seizures
Scenarios in which AED treatment should be considered

High risk profile for seizure recurrence
Remote symptomatic lesion and corresponding epileptiform EEG activity
*High risk lesion* (abscess, sinus thrombosis)

Neurobiological concept of “epilepsy”
- presence of epileptiform potentials on EEG, specifically generalized epilepsy

Medical and social conditions which lead to additional harm as a result of further seizures, examples:
- Polytrauma with spinal cervical fracture
- Severe osteoporosis
- Postictal renal failure due to myoglobulinemia
- Patients on anticoagulation
- Patients with high risk of loss of employment with further seizure

*Pohlmann-Eden and Legg 2013. Epileptology 1: 1-13*
Initial treatment: **Partial** onset epilepsy

Center-specific preferences: AED

- Lamotrigine
- Levetiracetam
- Carbamazepine

Based on expert opinion (level D), SANAD (level B) study, and level A studies (class I RCT DB 48 week studies)
Initial treatment: Primarily generalized epilepsy

Center-specific preferences AED

- Lamotrigine
- Valproate
- Levetiracetam
- Topiramate

Based on expert opinion (level D), SANAD (level B) study, **NO level A studies** (class I RCT DB 48 week studies)
HFSC: Halifax First Seizure Clinic
Profile
Patient Group Overview (n)

603
Overall Presentations

256
Excluded
PNES, syncope, TIA, migraine

177
FS
First Seizure

119
NOE
New Onset Epilepsy

51
NDE
Newly Diagnosed Epilepsy

Update October 2013
### Number of Seizures in treated NOE

<table>
<thead>
<tr>
<th>Seizure Count</th>
<th>Sz</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Sz</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>Sz</td>
<td>11%*</td>
</tr>
<tr>
<td>4</td>
<td>Sz</td>
<td>6%*</td>
</tr>
<tr>
<td>&gt;4</td>
<td>Sz</td>
<td>8%*</td>
</tr>
</tbody>
</table>

*No treatment: 8%

* all within last 12 mths

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**Unpublished data: Interim Analysis**
Halifax First Seizure Clinic, Update October 2013
Choice of AEDs used in New-onset Epilepsy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin*</td>
<td>37%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>19%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>18%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>15%</td>
</tr>
<tr>
<td>Valproate</td>
<td>6%</td>
</tr>
<tr>
<td>Others</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Often started by ER physician

**Unpublished data: Interim Analysis**
Halifax First Seizure Clinic, Update October 2013
Switch to **Second** AED in NOE < first 6 month

Switch in 37.7%

Safety/SE 41.4%

Not efficacious 27.5%

Other reasons 31.1%

> 50% switches: PTH to other AED (LEV in 75%)

*Unpublished data: Interim Analysis*
Halifax First Seizure Clinic, Update October 2013
Seizure-freedom after 6 months (1st follow-up)

Sz free with AED 64%
Sz free no AED 2%
One further sz 10%
Disabling sz $\leq 1$/mth 12%
Disabling sz $>1$/mth 2%

SPS only 10%

*Unpublished data: Interim Analysis*
Halifax First Seizure Clinic, Update October 2013
Failure of 2 or more AED suggesting Pharmacoresistance (PR)

149 patients with NOE and NDE, Interim Analysis: Occurrence of PR, Mean follow-up 2.6 years (2008-2012)
Halifax First Seizure Clinic,

Imhokhai Ogah AES 2012

Highly variable pattern of PR with sz-free intervals of > 1 year (demo)

11.2% only fulfilled criteria for PR
Patterns of Pharmacoresistance

33 y/o old female
Right periventricular gliosis, FCD?

56 y/o old female
Normal MRI

69 year old male
left arachnoid cyst
Illustrative case

42 y/o  M

- Treatment started with LEV BID 750mg
- 1 further GTCS after 3 months
- Dosage increase LEV BID 1,000mg
- No further sz within 3 year follow-up (188 weeks)

- MRI demo T2_FSE
- Periventricular Heterotopia
### Congenital malformations in 8 out of 224 patients with first seizure (FS), New-onset epilepsy (NOE), and newly diagnosed epilepsy (NDE)

FCD = Focal cortical dysplasia, PMG = polymicrogyria, HT = Heterotopia, TS = Tuberculosis sclerosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Imaging Diagnosis</th>
<th>Clinical Diagnosis</th>
<th>Follow-up Time (weeks)</th>
<th>AED</th>
<th>Seizure-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG</td>
<td>FCD</td>
<td>NDE</td>
<td>61</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SG</td>
<td>FCD</td>
<td>FS</td>
<td>49</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LB</td>
<td>FCD</td>
<td>FS</td>
<td>32</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>MJ</td>
<td>FCD</td>
<td>FS</td>
<td>27</td>
<td>_</td>
<td>+</td>
</tr>
<tr>
<td>CM</td>
<td>PMG</td>
<td>FS</td>
<td>46</td>
<td>_</td>
<td>+</td>
</tr>
<tr>
<td>KR</td>
<td>HT</td>
<td>NOE</td>
<td>188</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TA</td>
<td>HT</td>
<td>FS</td>
<td>161</td>
<td>_</td>
<td>+</td>
</tr>
<tr>
<td>KM</td>
<td>TS</td>
<td>NOE</td>
<td></td>
<td></td>
<td>Excellent overall prognosis both with and without AEDs</td>
</tr>
</tbody>
</table>

**Interim Analysis AES 2012 San Diego**
Halifax First Seizure Clinic
Treating New-onset Epilepsy

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Treating New-Onset Epilepsy: The Perspective of a Longitudinal Study

• **Precise definitions** of first seizure, new-onset epilepsy and newly diagnosed epilepsy in their temporal pattern are critical preconditions to interpret data in prospective studies dealing with early stages of epilepsy.

• Despite a center specific “rational algorithm” for individualized AED choice initiating treatment in NOE, “reality check” in our study showed that patients frequently end up with suboptimal AED as a result of health care system specifics or referral patterns. The epileptologist in charge may have to consider an early switch to a more appropriate AED.
Conclusions

Treating New-Onset Epilepsy: The Perspective of a Longitudinal Study

• Longitudinal studies in early stages of epilepsy allow a totally new perspective on current concepts of clinical epileptogenesis. Our preliminary data question current concepts (2 examples)

• Focal cortical dysplasia, heterotopia and other CM as identified by MRI may have a much better treatment prognosis than suggested in refractory treatment populations.

• Pharmacoresistance (PR) CANNOT be expected to always occur within the first year of diagnosis of NOE. It is much more likely that patterns of PR are much more variable and phases of seizure-freedom of 1 to 2 years or even longer may not exclude long-term PR. This observation has major counseling implications.
Thanks...!

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