Rigshospitalet

DET SUNDHEDSVIDENSKABELIGE FAKULTET
KØBENHAVNS UNIVERSITET

REGION

Treatment of epilepsy in young adults

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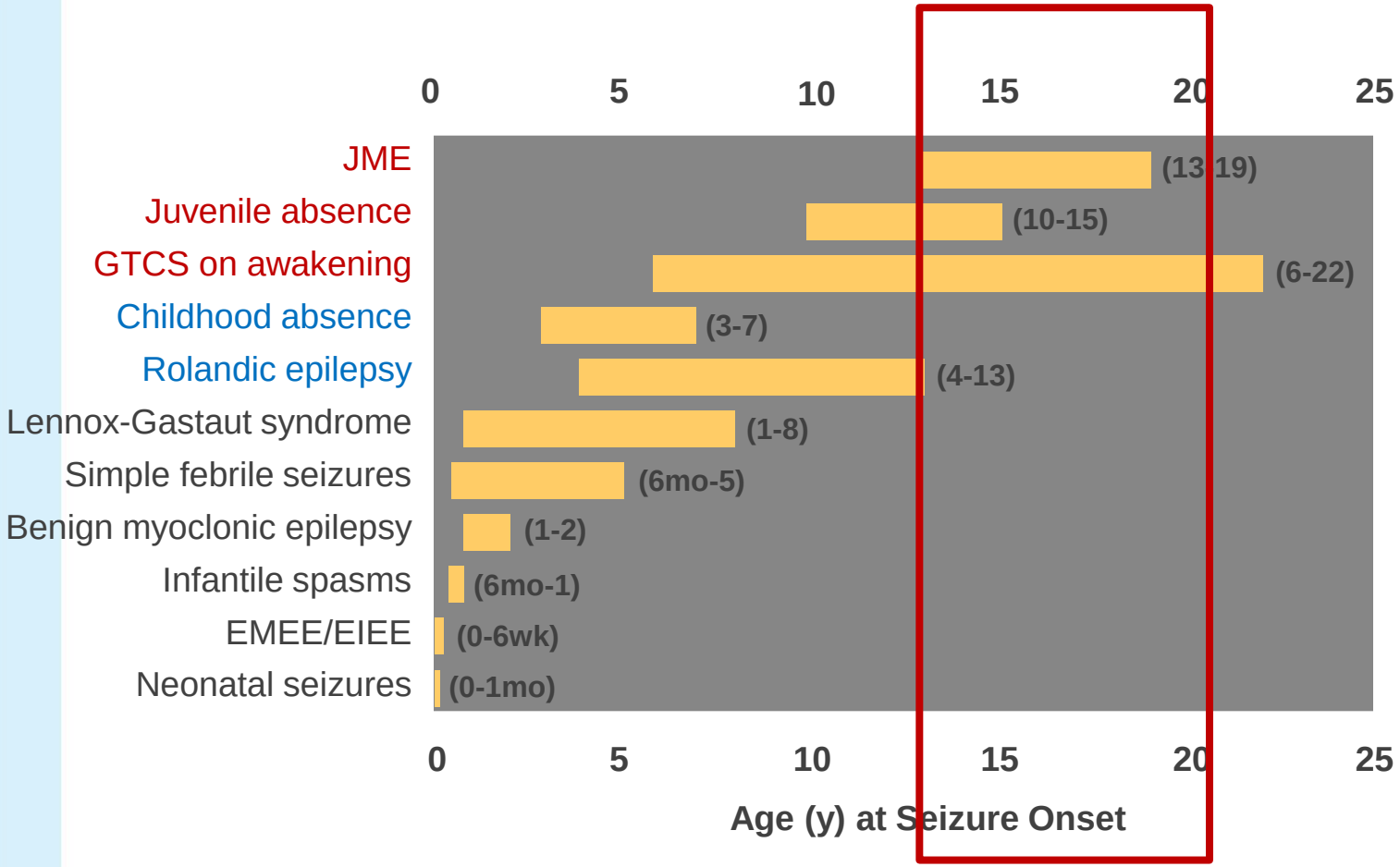
Objectives

- Teenage epilepsy
  - JAE & JME
  - Clinical symptoms
  - Diagnosis
  - Treatment
- Transition issues

- Incidence:
  - 11-19 y 20-60/100 000
  - < 11 y 4/1000 children with persisting epilepsy
- Prevalence:
  - 1/3 of all epilepsy patients are < 18 y

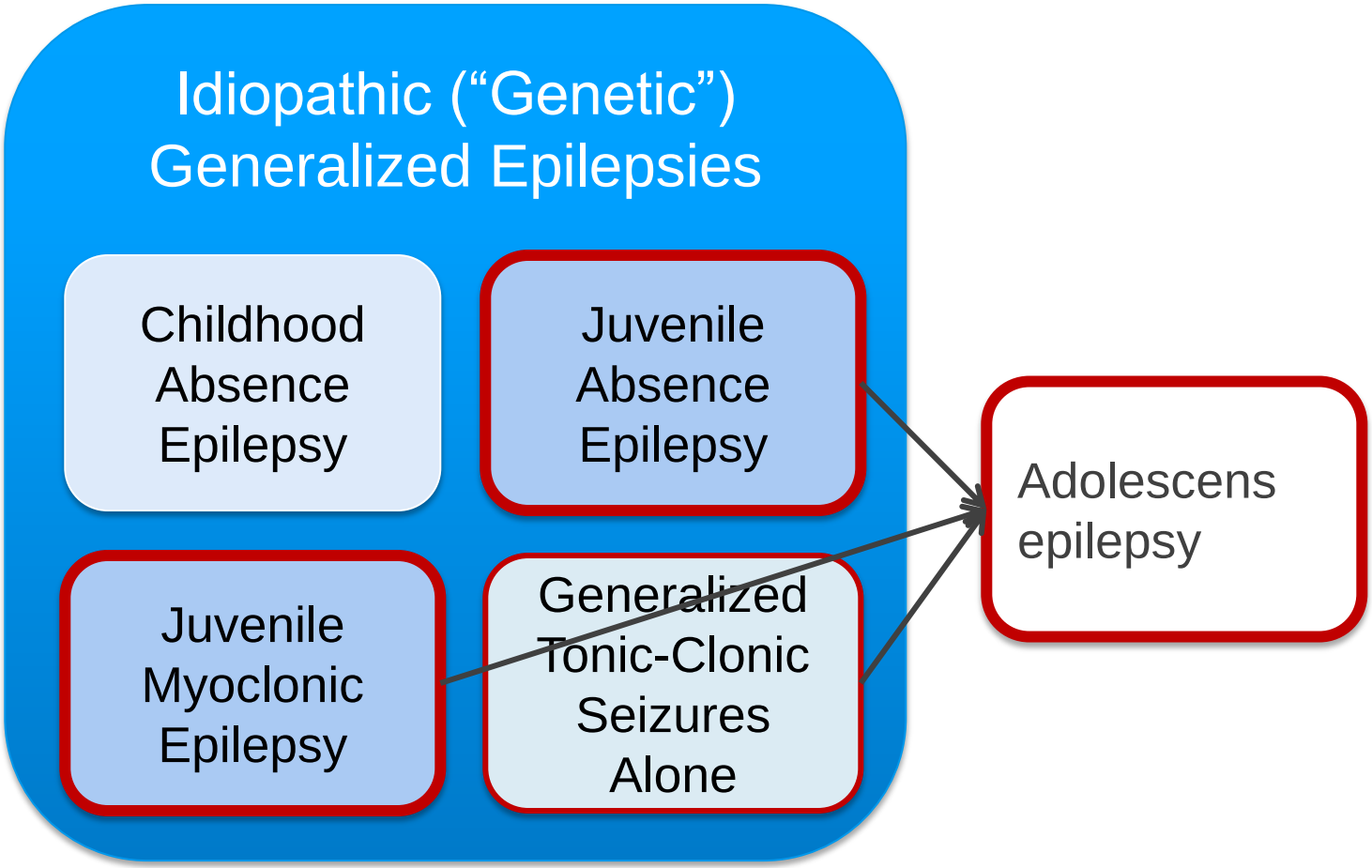
Christensen J., et al.: Epilepsy Res 2007
Appleton RE.; Seizure 1995

Epilepsy syndromes



IGE affects apprx. 15-20% of all patients with epilepsy

(Jallon and Latour, 2005)



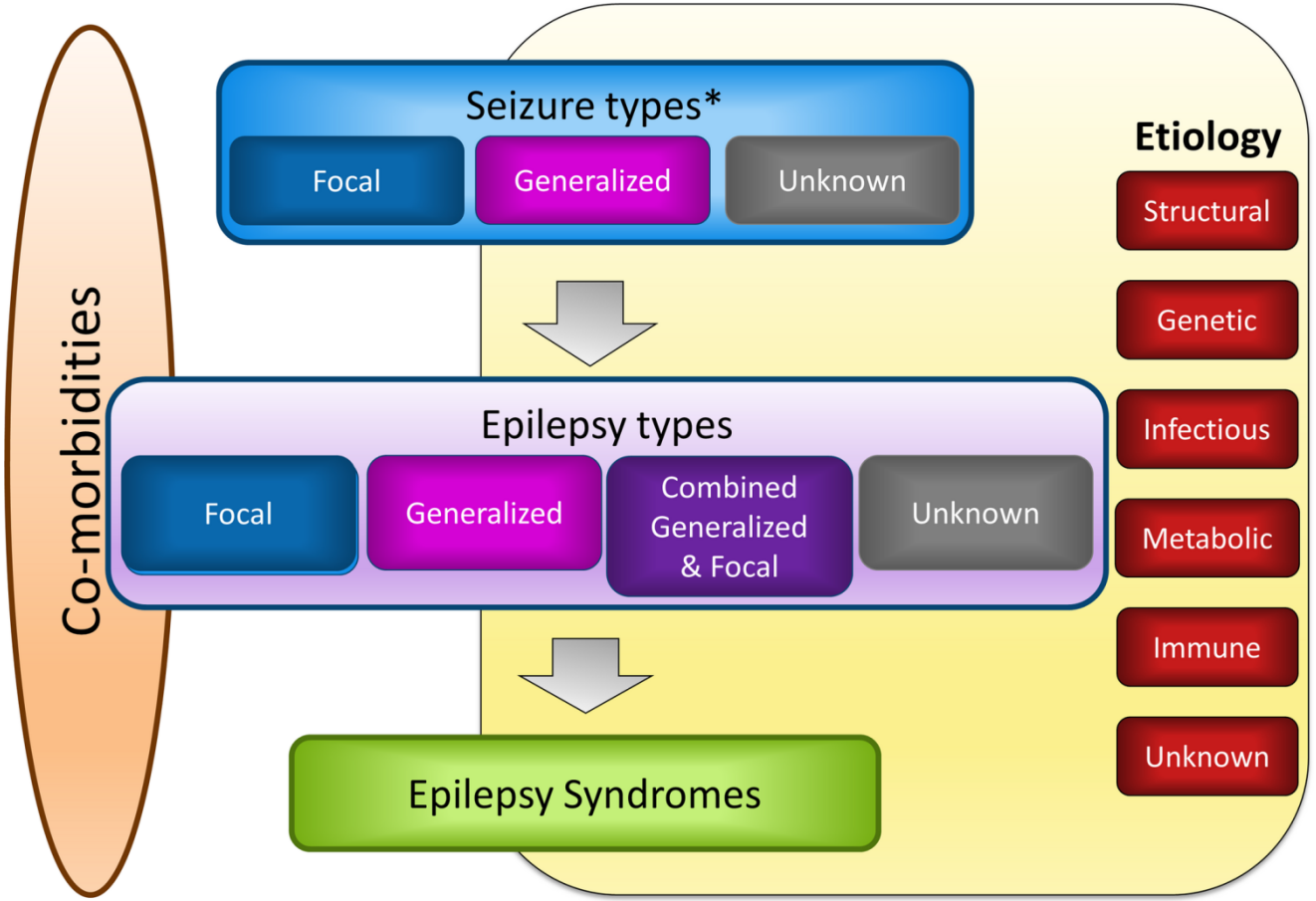
Genetic *versus* idiopathic

- 'Idiopathic' = presumed hereditary predisposition

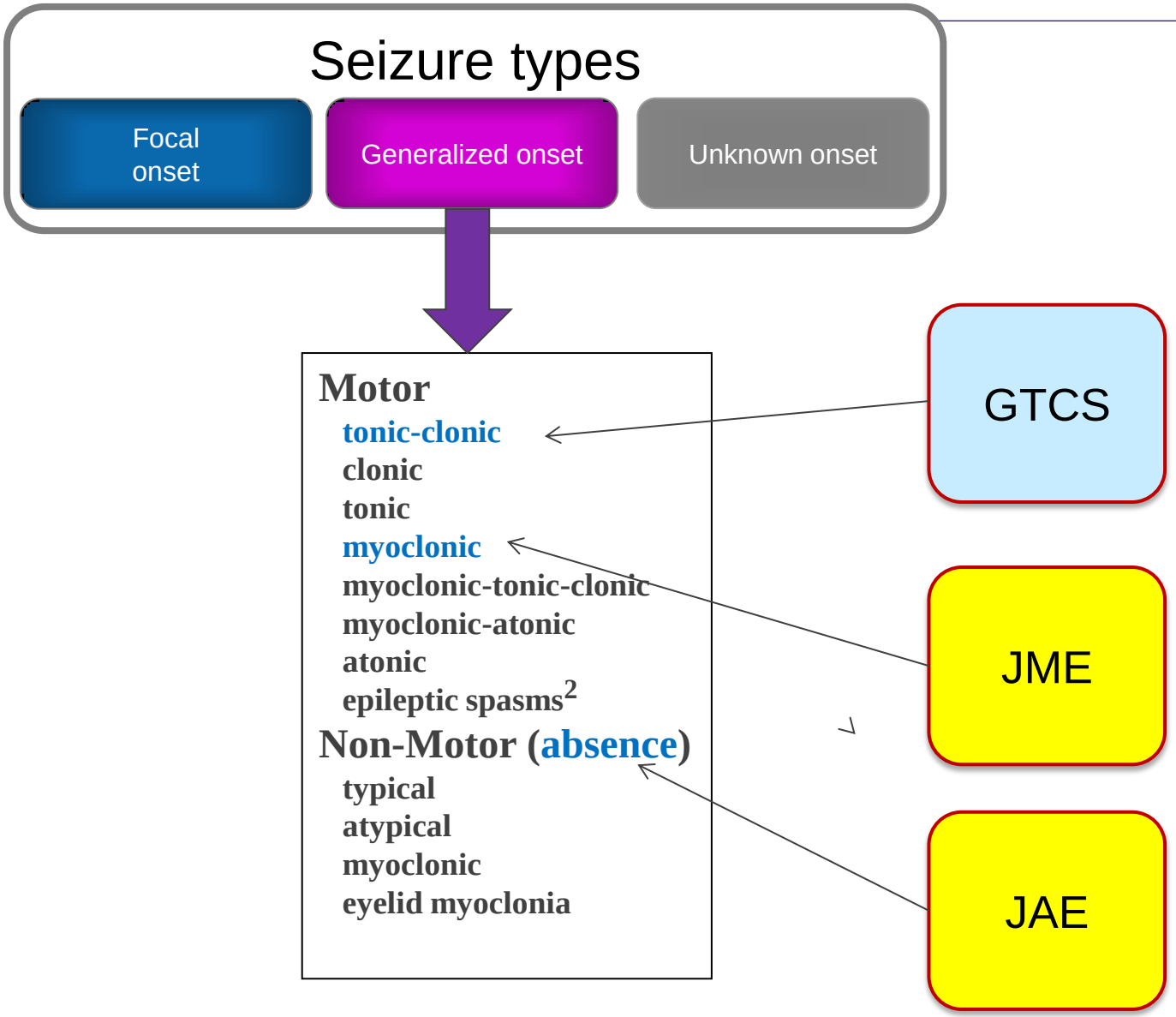
- Genetic ≠ inherited
  - Importance *of de novo* mutations in both mild and severe epilepsies

- Critical problem of stigma in some parts of the world

ILAE classification of the epilepsies



ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology, Volume: 58, Issue: 4, Pages: 512-521, First published: 08 March 2017, DOI: (10.1111/epi.13709)

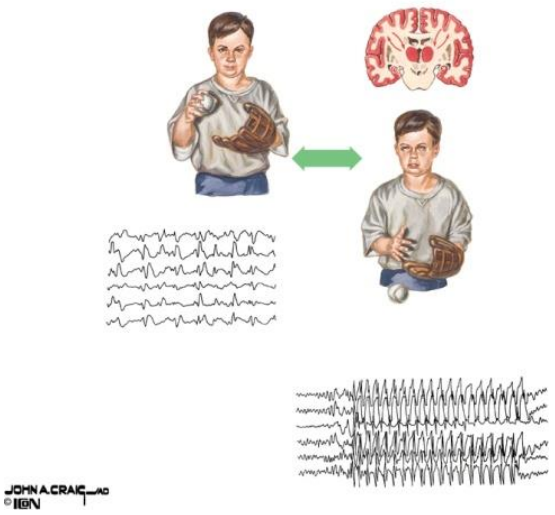

Seizure types
Focal onset
Generalized onset
Unknown onset
Motor
tonic-clonic
clonic
tonic
myoclonic
myoclonic-tonic-clonic
myoclonic-atonic
atonic
epileptic spasms[2]
Non-Motor (absence)
typical
atypical
myoclonic
eyelid myoclonia
GTCS
JME
JAE

Juvenil absence epilepsy

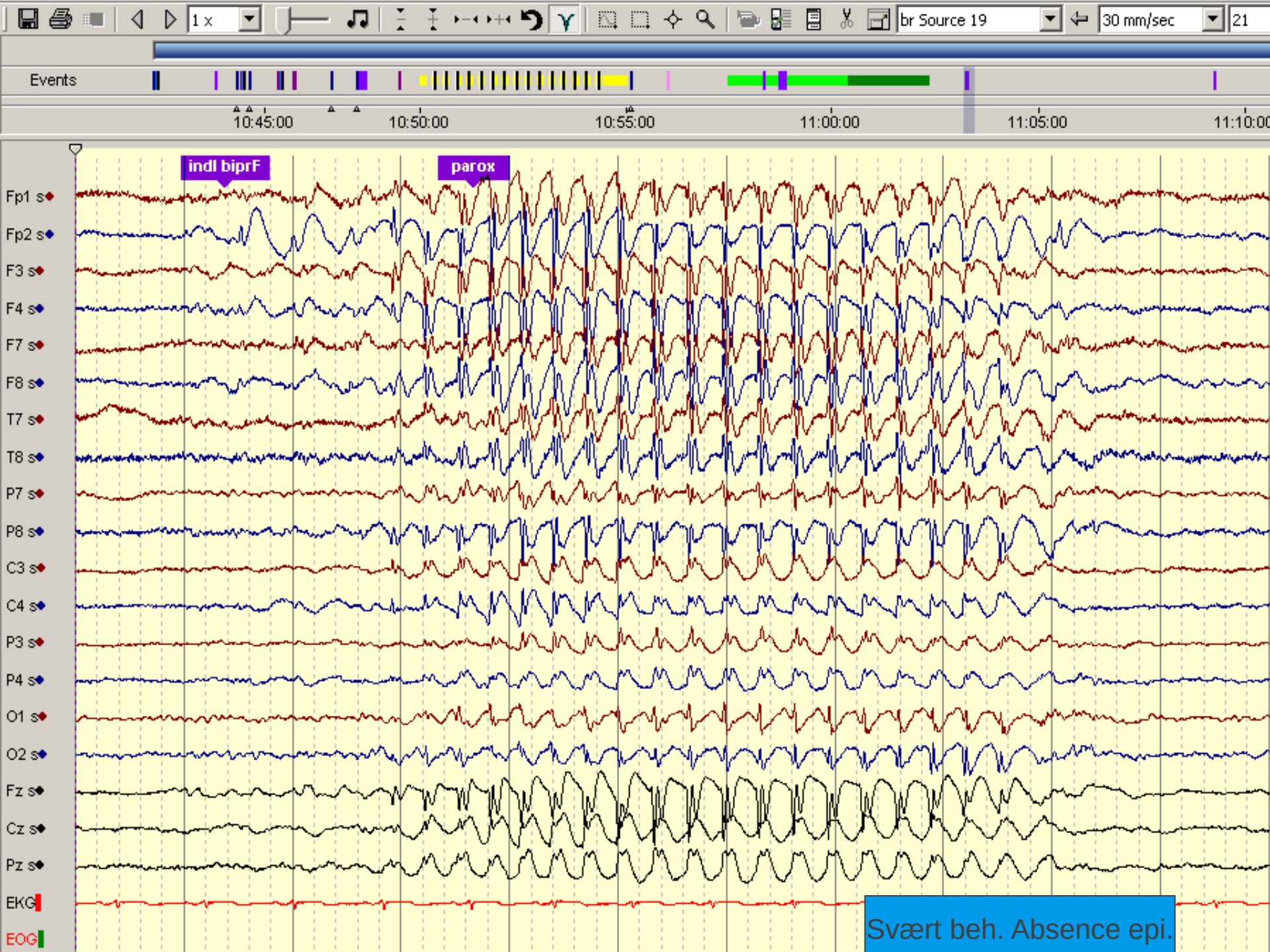
- Genetic generalized epilepsies
- CAE/JAE differs by seizure frequency
- Incidence:
  - 2–3% of patients with adult epilepsy,
  - 8–10% of IGE
- Age of onset 8-20 y (9-13) of age
- No sex dominance
- Needs life-long treatment

- ✓ **Absence seizures**
- ✓ Not very frequent seizures
- ✓ *GTCS may occur prior to ABS*
- ✓ *GTCS during the course (80%)*
- ✓ *Myoclonic jerks can occur (10-20%)*

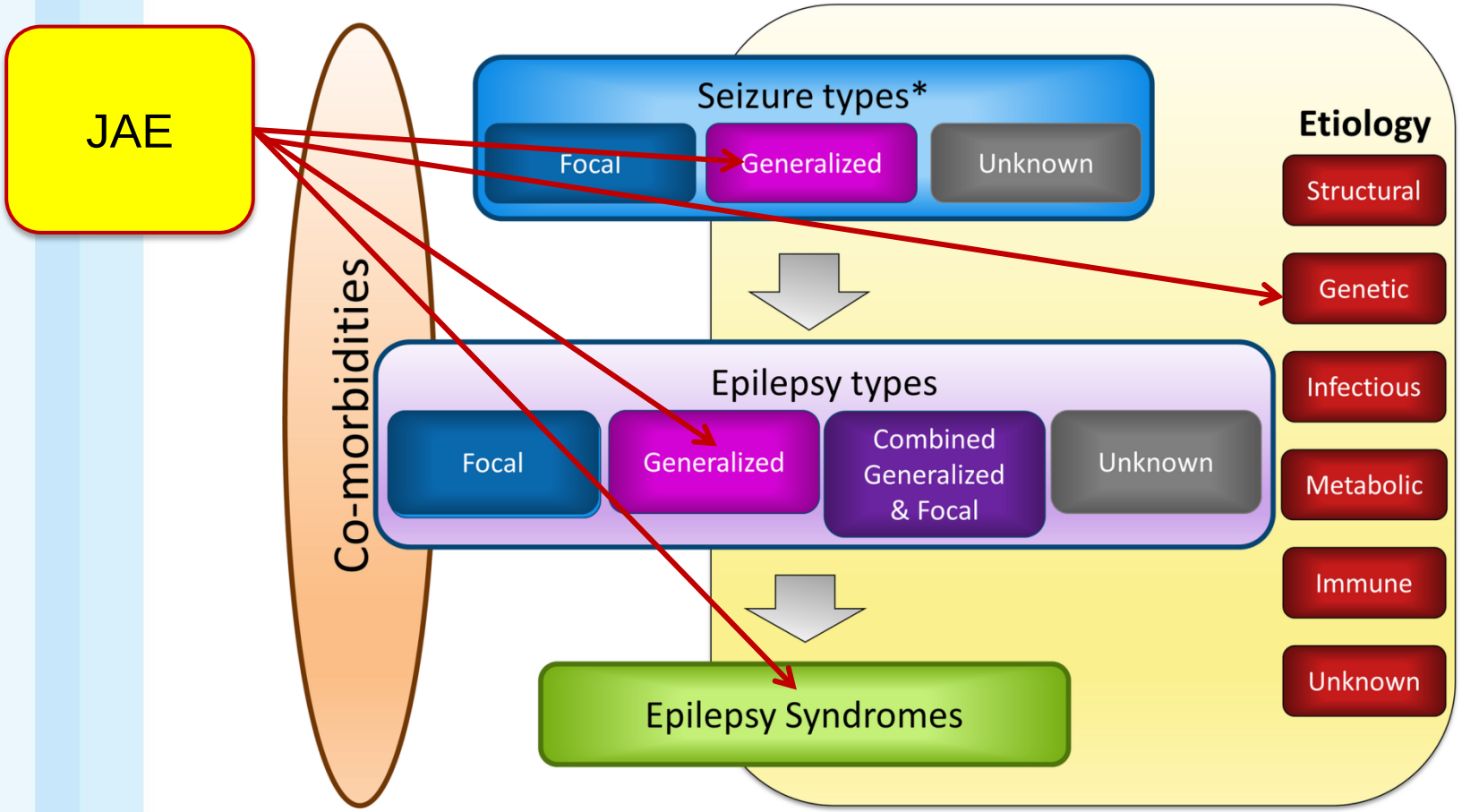
Typical absence - EEG



- Usually regular and symmetrical 3 Hz (2-4 Hz) spike-and-slow-wave complexes and may have multiple spike-and-slow-wave complexes.
- Abnormalities are bilateral, synchronous.
- Background activity: usually normal (occasionally: focal EDs; bilateral, occipital slowing)


1 x
br Source 19
30 mm/sec
21
Events
10:45:00
10:50:00
10:55:00
11:00:00
11:05:00
11:10:00
indl biprF
parox
Fp1 s
Fp2 s
F3 s
F4 s
F7 s
F8 s
T7 s
T8 s
P7 s
P8 s
C3 s
C4 s
P3 s
P4 s
O1 s
O2 s
Fz s
Cz s
Pz s
EKG
EOG
Svært beh. Absence epi.

ILAE classification of the epilepsies



ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology, Volume: 58, Issue: 4, Pages: 512-521, First published: 08 March 2017, DOI: (10.1111/epi.13709)

Juvenil myoclonic epilepsy

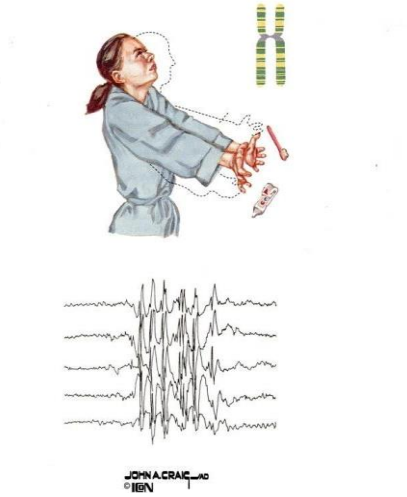
- Genetic generalized epilepsies
- Prevalence of 5-11 % among all patients with epilepsy
- Age of onset in the adolescence
- Female predominance
- Often need life-long therapy

- ✓ **Myoclonic jerks (MJ)**
- ✓ Fully conscious state
- ✓ Predominate in the upper limbs
- ✓ Usually on awakening.
- ❖ *GTCS may occur in 50–80%*
- ❖ *Absences in only 15–30% (?)*

Myoclonia: Sudden, brief (<100 ms) involuntary, single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).

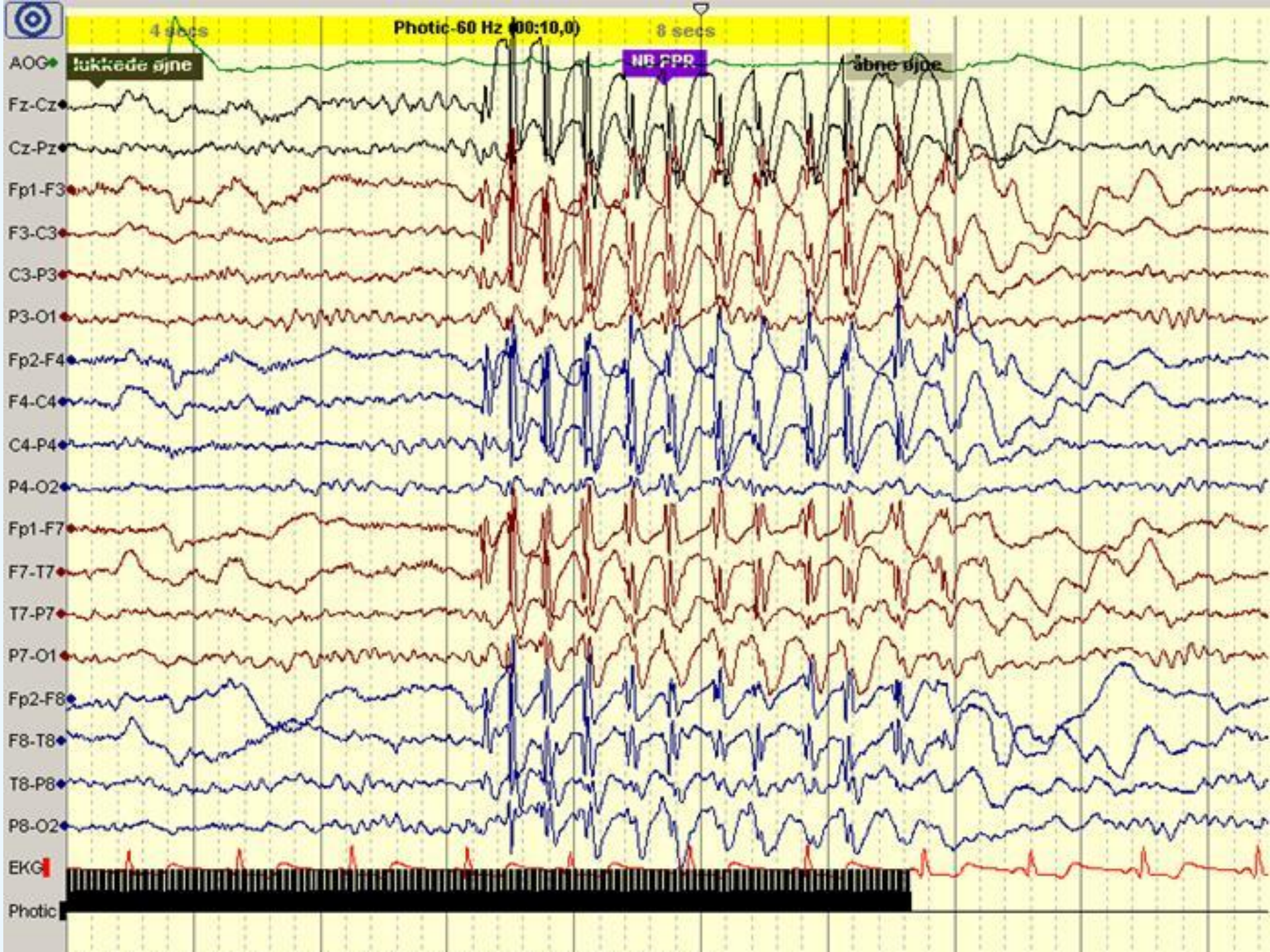
JME: Characterized by mandatory or typical myoclonic seizures alone or combined with generalized tonic–clonic seizures (GTCS) and/or absence seizures (ABS)

JME - EEG

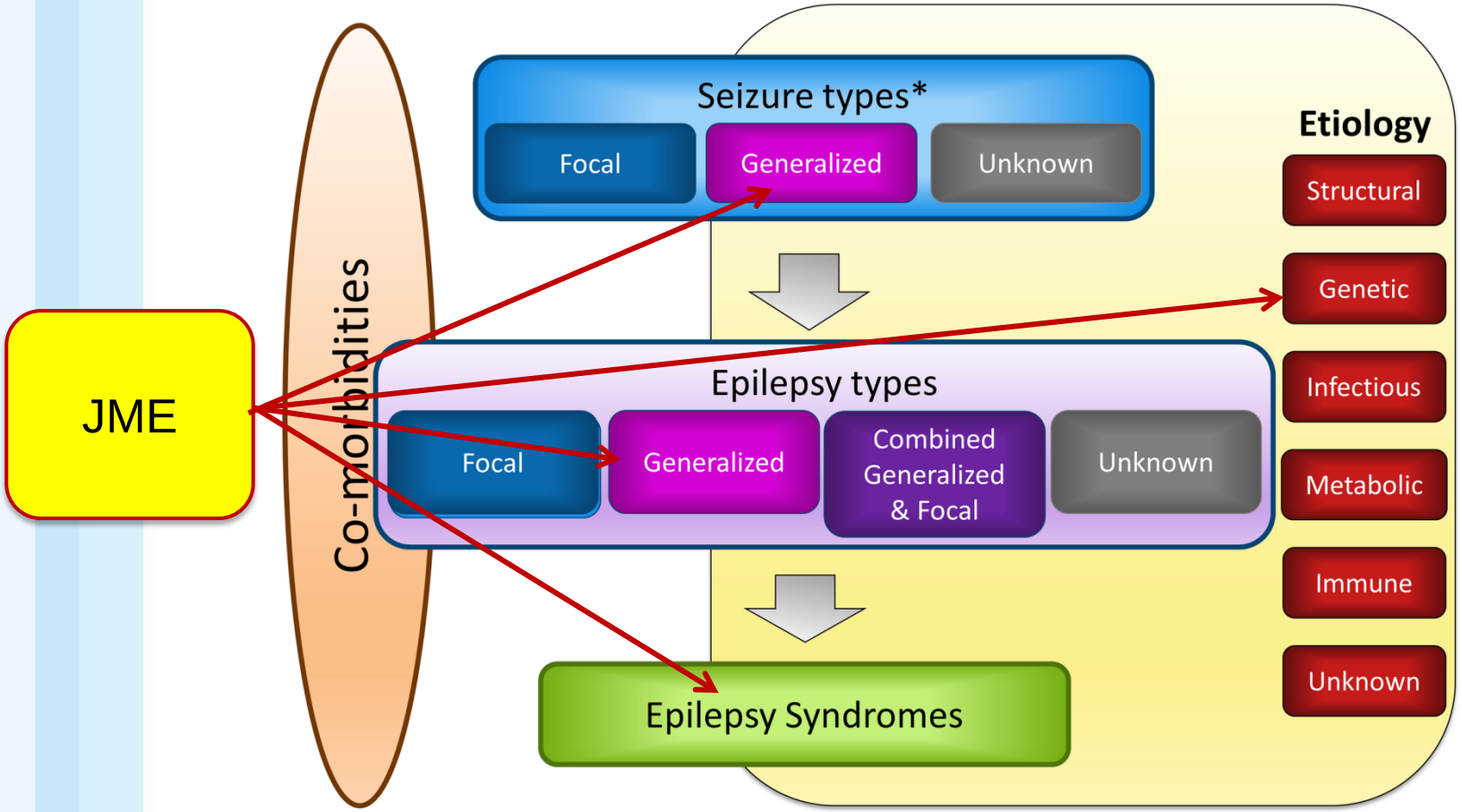


- Generalized spikes, polyspikes, spike-wave complexes, or combinations of these

- Provoking factors for JME discharges
  - Higher mental activities like **speaking, reading, writing, arithmetic calculation, and spatial construction** (Matsuoka et al., 2000)
  - Perioral reflex myoclonias induced by either **reading or speaking** (Mayer et al., 2006),
  - Photoconvulsive responses (30%)


4 secs
Photic-60 Hz (00:10,0)
8 secs
AOG
lukkede øjne
NB EPR
åbne øjne
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
EKG
Photic

ILAE classification of the epilepsies



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G. Cação et al. / Epilepsy & Behavior 82 (2018) 81–86

Box 1

Juvenile myoclonic epilepsy (JME) diagnostic criteria and clinical phenotypes.

Diagnostic criteria for JME (adapted from Kasteleijn-Nolst Trenité DG et al, Epilepsy Behav 2013 [5])	
Class I	1. Myoclonic jerks without loss of consciousness repeatedly occurring on awakening, i.e., within 2 h after awakening 2. EEG (routine, sleep, or sleep deprivation) that shows normal background and ictal generalized high amplitude polyspikes (and waves) with concomitant myoclonic jerks 3. Normal intelligence 4. Age at onset of between 10 and 25 years
Class II	1. Myoclonic jerks predominantly occurring on awakening 2. Myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual stimuli and praxis or GTCSs preceded by myoclonic jerks 3. EEG shows a normal background and at least once interictal generalized spike or poly-spike and waves with some asymmetry allowed with or without myoclonic jerks 4. No mental retardation or deterioration 5. Age at onset of between 6 and 25 years
JME clinical phenotypes (adapted from Martínez-Juárez IE et al, Brain 2005 [9])	
Classic JME	Adolescence onset of myoclonic, tonic-clonic and clonic-tonic-clonic seizures with or without rare-to-infrequent absences and an EEG with 4–6 Hz polyspike-wave complexes
CAE evolving to JME	Onset with absences with 3–4 Hz spike and wave complexes before aged 12 and then developed JME
JME with adolescent absence	Onset with absences with 3–5 Hz spike and polyspike and wave complexes aged 12 or older mixed with JME
JME with astatic seizures	Astatic seizures mixed with JME

Prognosis of JME

- Benign epileptic syndrome
- Easy to control seizures
- Lifelong therapy is often needed

Large cohort study:

- N=6600 patients with epilepsy
- N= 240 JME
- Only 48% of patients were seizure free in the previous year
- Refractory cases (30-50%), 25% of them were seizure free in the previous year

	Refractory	Non-refractory	
Follow-up			<0.05
Sz free	30 (25%)	84 (71%)	
Only MJ or Abs	14 (11%)	16 (13%)	
GTCS +/− MJ or Abs	69 (57%)	15 (13%)	
Lost to follow-up or death	8 (7%)	4 (3%)	

Epilepsy & Behavior 82 (2018) 81–86

Table 1
Clinical and demographic characteristics.

Number of patients	240
M:F ratio	94:146
Current age (y)	38 (SD 11.7)
Age at sz onset (y)	14.2 (SD 4.5)
Age at diagnosis (y)	15.6 (SD 4.9)
Clinical phenotype	
Classic	212 (88%)
CAE evolving into JME	14 (6%)
JME with adolescent Abs	9 (4%)
JME with astatic sz	5 (2%)
Past medical history	
Febrile convulsions	10 (4%)
Delayed language development	5 (2%)
Prematurity	5 (2%)
Asperger's syndrome	3 (1%)
Type 1 DM	4 (2%)
Nonrelevant	175 (73%)
Family history of epilepsy	
JME in first degree	3 (1%)
Non-JME in first degree	35 (15%)
JME in other members	3 (1%)
Non-JME in other members	26 (11%)

M — male; F — female; y — years; sz — seizures; CAE — childhood absence epilepsy; JME — juvenile myoclonic epilepsy; Abs — absences; DM — diabetes mellitus.

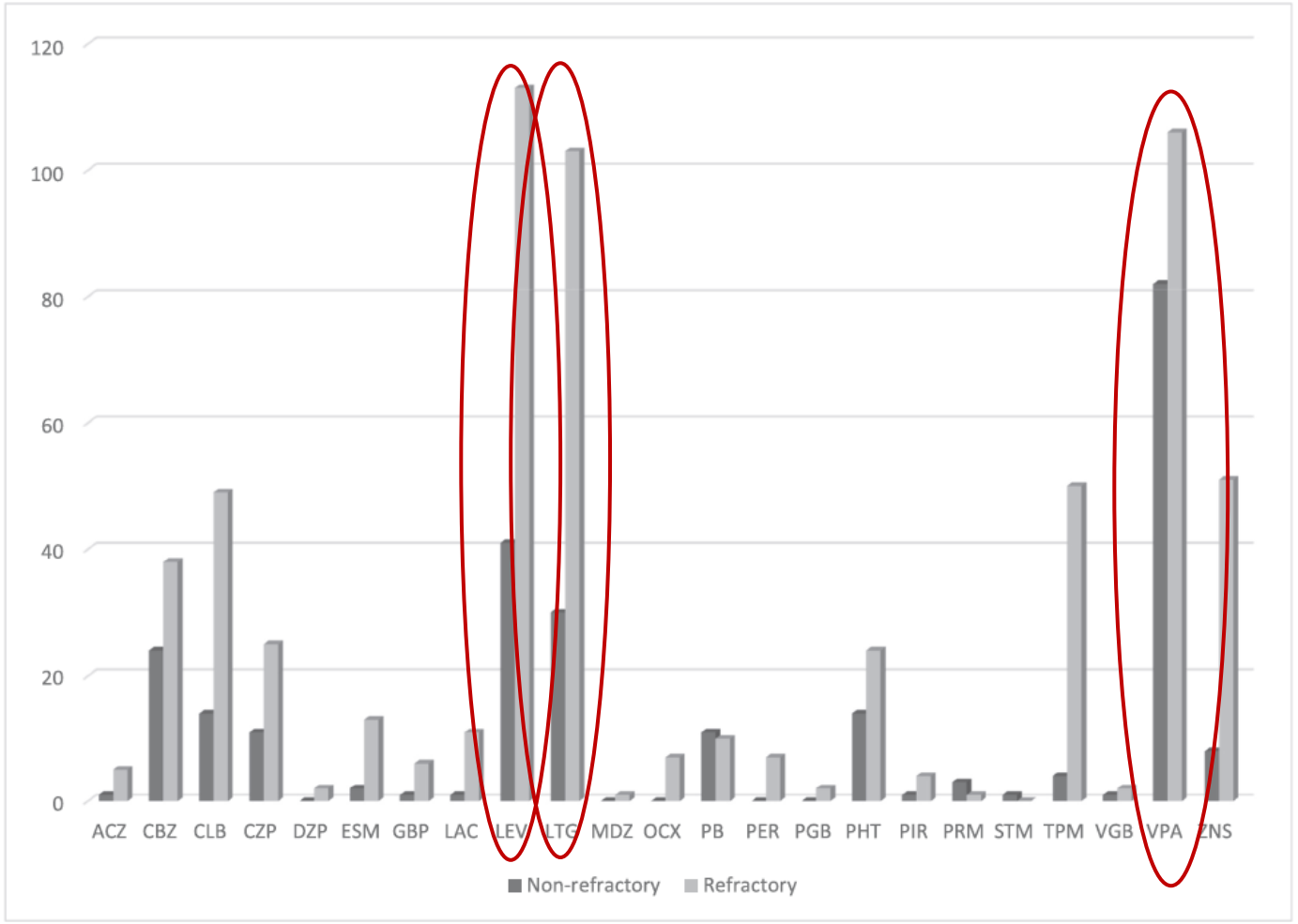


Fig. 1. Total AED used in the group with refractory seizures and the group with nonrefractory seizures. Legend: Total number of each AEDs ever prescribed in the group with refractory seizures and the group with nonrefractory seizures. ACZ — acetazolamide, CBZ — carbamazepine, CLB — clobazam, CZP — clonazepam, DZP — diazepam, ESM — ethosuximide, GBP — gabapentin, LAC — lacosamide, LEV — levetiracetam, LTG — lamotrigine, MDZ — midazolam, OXC — oxcarbazepine, PB — phenobarbital, PER — perampanel, PGB — pregabalin, PHT — phenytoin, PIR — piracetam, PRM — primidone, STM — sulthiame, TPM — topiramate, VGB — vigabatrin, VPA — valproic acid, ZNS — zonisamide.

Epilepsy & Behavior 82 (2018) 81–86

Remission and relapse of JAE and JME

- **Remission rates**
  - JME : 33 to 88%
  - JAE : 21–89% .
- **Relapse rate**
  - JAE and JME similar
  - High (80-100%) for both groups who had been in remission, after AED withdrawal
  - Lack of long-term data

Seizure: 2018 Jul;59:116-122.

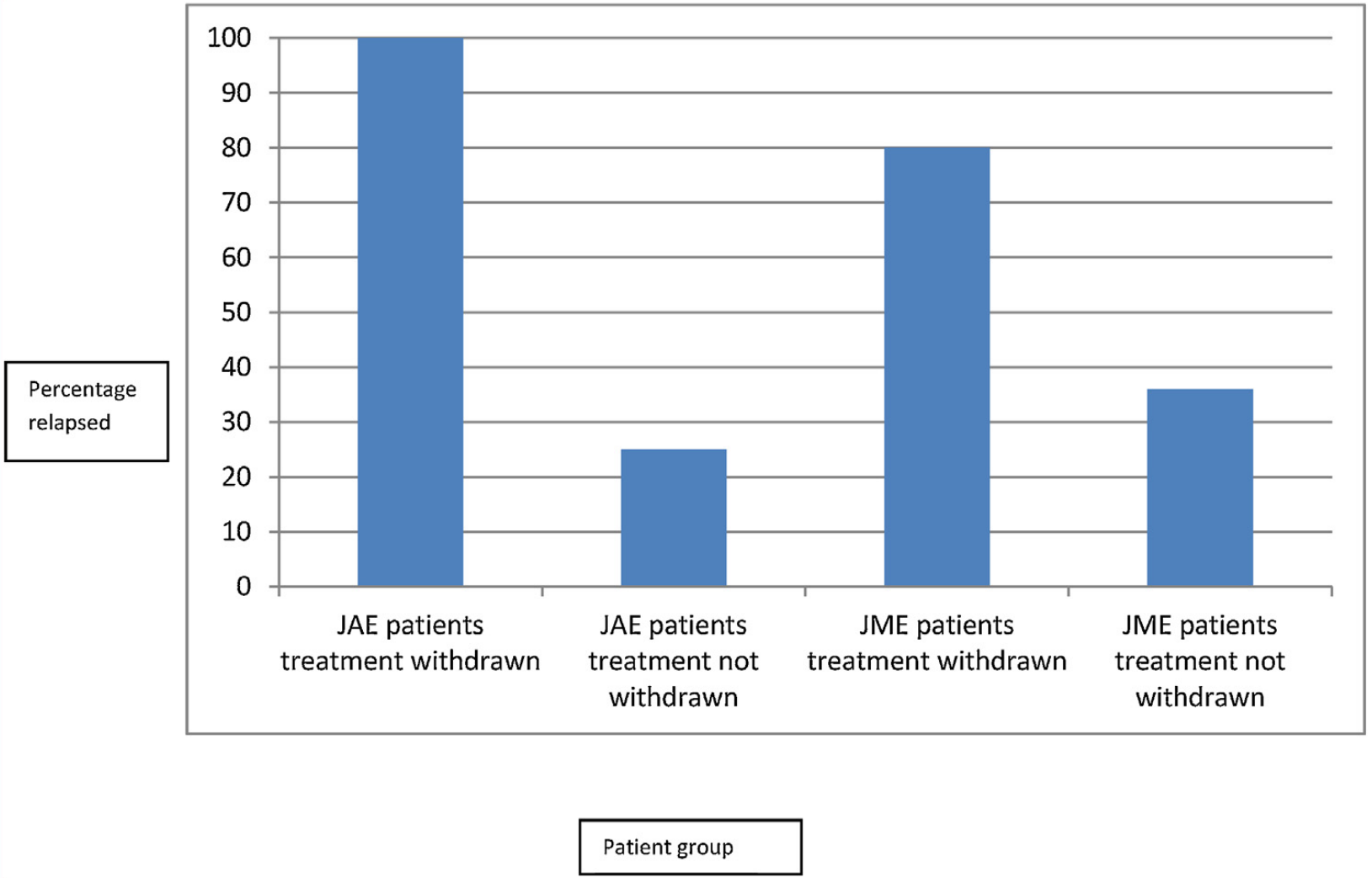


Fig. 3. Relapse% observed in those withdrawn and not withdrawn from AEDs, after at least 2 years seizure freedom.

L. Healy et al. / Seizure 59 (2018) 116–122

Remission and relapse of JAE and JME

- **Remission rates**
  - JME : 33 to 88%
  - JAE : 21–89% .
- **Relapse rate** for both JME and JAE patients who had been in remission, after AED withdrawal (long-term??)

- **Conclusion:**
  - Remission rates for JAE and JME was lower than expected.
  - Relapse rates off AEDs were similar for JAE and JME, and at least twice as high as for those remaining on AEDs,
  - Further remission was not invariable on restarting AEDs

Seizure: 2018 Jul;59:116-122.

Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25–63 years of follow-up

*Julia Geithner, *Felix Schneider, †Zhong Wang, *Julia Berneiser, *Rosemarie Herzer, *Christof Kessler, and *Uwe Runge

*Department of Neurology, Epilepsy Center, University of Greifswald, Greifswald, Germany; and †Cleveland Clinic Epilepsy Center, Neurological Institute, Cleveland, Ohio, U.S.A.

The aim:

- to investigate the long-term seizure outcome in patients with JME after a follow-up of at least 25 years and
- to identify factors that are predictive for the seizure outcome.

Poor prognosis

- GTCS preceded by BMJ
- Long duration until seizure freedom is reached
- Polytherapy

Favorable prognosis

- Remission of GTCS under AED treatment is predictive of a long-term seizure-free outcome.
- The occurrence of PPRs significantly increase the chance of seizure recurrence after AED discontinuation.
- A shorter duration of epilepsy until seizure freedom is reached.

Epilepsia, 53(8):1379–1386, 2012

Management of epilepsy in teens

”Transition” and ”transfer” from pediatric to adult care

- Dynamic, planned and structured process
- Between age 12-18
- Where to transfer patients?
  - GP/specialist/hospital service
  - Adult neurologist’s experience in dealing with ”adult issues” (sex, contraception, pregnancy, driving, employement regulations, etc.)
  - Pædiatricians experience in treating childhood epilepsies
  - Children with learning disabilities
  - Patients interest - FOCUS
- Transition clinic – organisation/staff

Patient population in adolescent

- Epilepsy since childhood (50% persists)
- Newly diagnosed epilepsy in teens
- Recidive childhood epilepsy

Adolescent

Chronic disease

- Brain
- Puberty
- Sexuality
- Psychological
- Bone health

- Treatment
- Stigma
- Dependence
- Comorbidity
- Social problems

Quality of life along life span

- Seizure
- Comorbidity
- Psycho-social factors

TAKING OVER EPILEPSY FROM THE PAEDIATRIC NEUROLOGIST

Philip E M Smith, Sheila J Wallace

J Neurol Neurosurg Psychiatry 2003;**74**(Suppl I):i37–i41

Box 1: Principles of consulting with teenagers with epilepsy

- See the teenager in a clinic setting with other teenagers or adults
- Focus the consultation on the teenager rather than the parents—for example, invite the teenager to introduce their parents or carer
- Discuss with the teenager adult topics such as alcohol, driving, pregnancy, and contraception
- Speak to the teenager alone during the consultation; an opportunity arises if the physical examination is conducted in another room
- Give the opportunity to speak to an epilepsy specialist nurse; like many adults, teenagers often open up to a nurse more than to a doctor
- Offer written material on relevant aspects of epilepsy. Sending copy letters to patients empowers them and acts as continuing education and encouragement
- Encourage carers to allow the teenager an appropriate amount of responsibility—for example, for his or her own tablets

Transition clinic – staff

Pediatrician
Neurologist
Epilepsy nurses

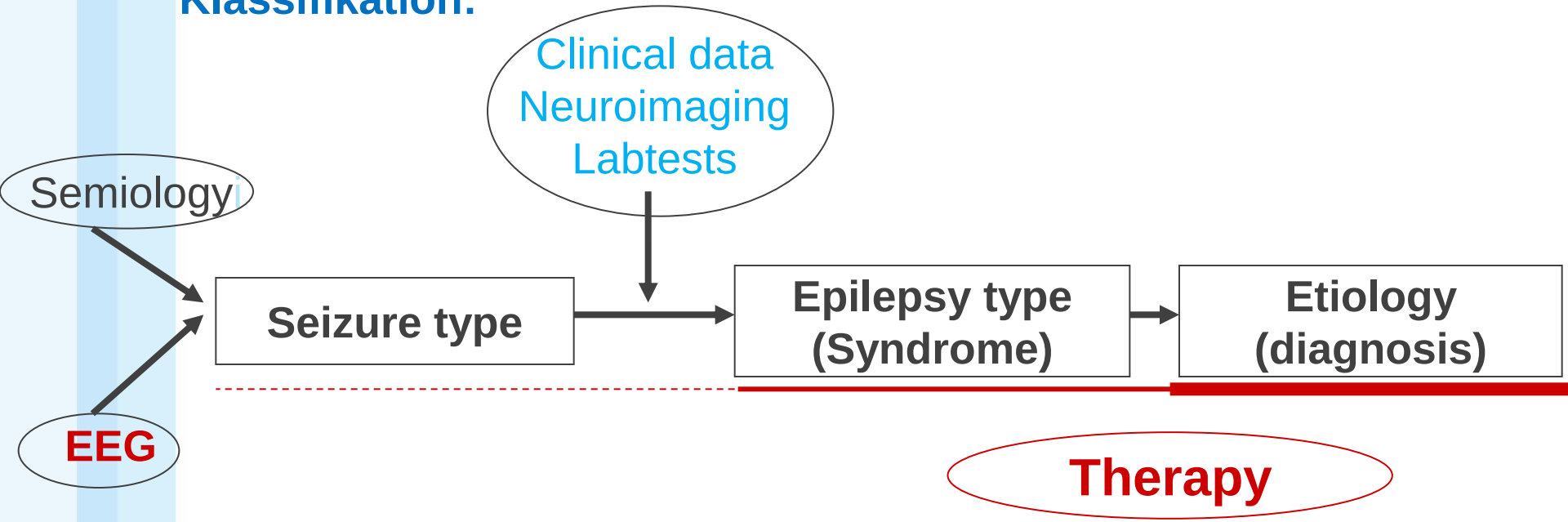
Psychologist
Psychiatrist
Social worker

Diagnosis & classification

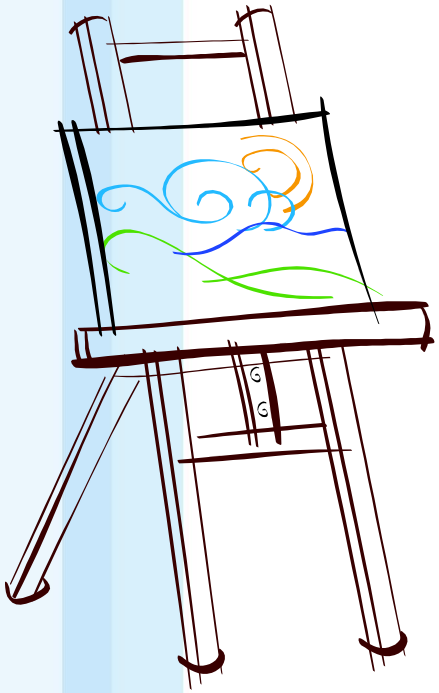
History

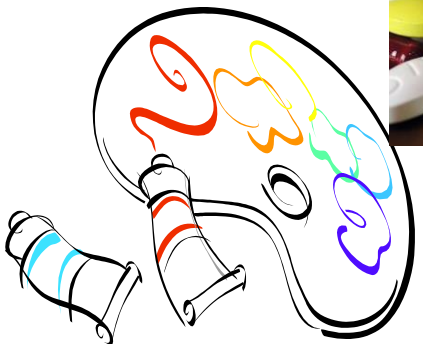
- Seizure description (semiology)/video film
- Clinical symptoms/neurological signs (cognitive function)
- EEG
- MRI (SPECT, PET)
- Laboratory tests (genetic)

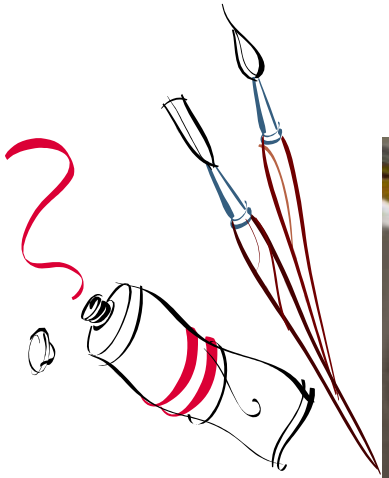
Klassifikation:



The Art of Antiepileptic Treatment







Matching the Drug to the Patient

Treatment

- No principal differencies in treatment strategies
  - Seizure freedom
  - Monotherapy
  - Side-effect profile (weigth, psychic, cosmetic)
  - Interactions (p-pills)
- Targeted treatment (JME/JAE)
- Identify medical intractability
- Involving the teens in decision making
- Information, education, life style

Case 2 /UB

- Normal birth, development, fam. disp.: non

- Epilepsy since 13 y of age – dg 2 years later, JAE
  - Sz types: absences, no GTCS
  - EEG: gen. paroxysms of SPW complexes 3,5-4 Hz
  - MRI norm.

- Th: LTG+VPA
  - No side-effects
  - SZ free (??)
- Comorbid depression (fam.)

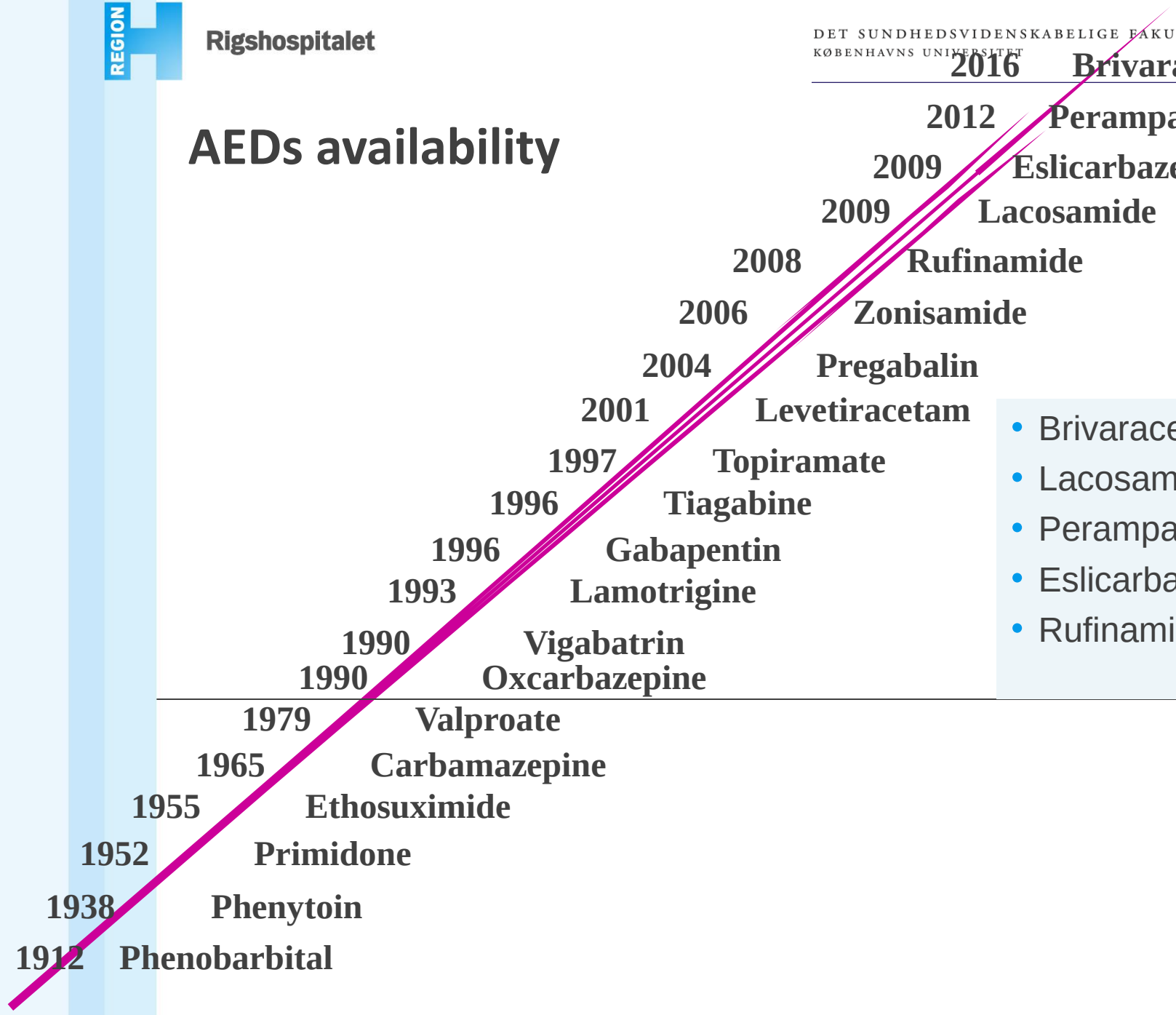
UB cont.

- Transition in 2014 (19 y)
  - SZ-free??
  - Compliance
  - Cognitive problems
- 2016-17
  - Tendence to absences- precipitated often
  - Never been SZ free
  - Th: LTG 200 mg + VPA 1500 mg
  - Needs immediate help
  - vEEG
  - Therapy changed: VPA → LEV → ESM (+LTG)
  - NEW: GTCS ??

Inflencing factors on choosing AED

AED-specific factors	Patient-specific factors	Country-specific factors
• **Sizure type or epilepsy syndromes** • Dose-dependent AE • Toxicity • Teratogenicity • Carcinogeniciyty • Pharmacokinetic • Interactions • Administration forms	• Genetic background • Age • Gender • Comedication • Comorbiditet • Insurrance	• AED availability • AED prices • Insurrance

AEDs availability



- Brivaracetam > 4 y
- Lacosamide > 4 y
- Perampanel >12 y
- Eslicarbazepine > 6 y
- Rufinamide >4 y

2013

Epilepsia, **(*):1–13, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE subcommission of AED Guidelines

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Summary of Evidence and Recommendations

Generalized onset seizures

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
GTC: Adults	0	0	23 4	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
GTC: Children	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Absence seizures	0 1	0	6 1	Level A: (None), *ESM, VPA Level B: None Level C: (ESM), LTG, (VPA) Level D: None *may aggravate GTCS

Summary of Evidence and Recommendations

Epilepsy syndromes

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
BECTS	0	0	2 1	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
JME	**0**	**0**	**0** **1**	**Level A: None** **Level B: None** **Level C: None** **Level D: CZP, LTG*, LEV, TPM, VPA, ZNS** **Level E: Others** **Level F: CBZ*, GBP, OXC*, PHT*, TGB, VGB** ***may aggravate myoclonic seizure types, should be used with caution**

Diagnosis and management of epilepsies incl. recommendations for the pharmacological treatment of JME.

- ✓Absolut 1st line: Valproic acid
- ✓1st line: lamotrigine, levetiracetam and topiramate
- ✓ 2nd line: lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive therapy
- ✓3rd line: clobazam, clonazepam or zonisamide

Valproate in the treatment of epilepsy in women and girls

Pre-Publication: Summary of Recommendations from a joint Task Force of ILAE-Commission on European Affairs* and European Academy of Neurology (EAN)** - 2015 (www.ilae.org)

The UK National Institute for Health and Care Excellence (NICE) guidelines (2017)

AEDs negative effect

Absences

- Carbamazepine
- Oxcarbazepine
- Eslicarbazepine (?)
- Phenytoin
- Gabapentin
- Pregabalin
- Tiagabin
- Vigabatrin
- Primidon(?)

Myoclonia

- Carbamazepine,
- Oxcarbazepine,
- Eslicarbazepine (?)
- **Lamotrigine**
- Gabapentin
- Pregabalin
- Tiagabin
- Vigabatrin

Case 1 / DS

- Debut i 11 y (2004)
- JAE: Absencer og seldom GTCS
- EEG (2010): 4-5 Hz generalized paroxysms with PSW, precipitated by HV (IGE)
- Therapy:
  - 2004 Lamotrigine – not sufficient
  - 2008 Ethosuximid additive (+clobazam) – still not SZ-free
- Clinical symptoms:
  - Still not Szfree
  - myoclonic jerks??,
  - sleep problems
- Polysomnography: norm.
- Therapy:
  - Lamotrigine for epilepsy
  - Melatonin for sleepidisturbance
  - Sifrol (obs. restless-leggs)

REVISION of diagnosis and treatment

- 2012 – referred to Glostrup
  - Suspect for side-effects for LTG
  - vEEG SWP, myoclonia with norm. ictal EEG, no clinical SZ but interictal PSW .
  - New PSG – norm

- Shift from LTG to LEV + ETX → SZ free,
- Withdrawal of Sifrol → no myoclonia anymore

Improved of quality of life in the last 5 years!

Concluding remarks

Transition

Social issues

Family

Driving

Education

Comorbidity

Diagnostic challanges

Quality of life

Targeted treatment

Compliance

Withdrawal