Are They Benign as Being Named?

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Epilepsy Syndromes

Clinical entity with relatively consistent clinical features, including seizure type(s), etiology, EEG features, neurologic status, prognosis, in some cases- response to specific antiepileptic drugs.

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Advantage of Determination of Electro-clinical Syndrome

- Drives the etiologic evaluation
- Determines the best choice AED
- Suggests duration of AED therapy
- Broad forecasts the prognosis
- Useful tool for genetic linkage analysis

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Types of Epilepsy of Good Prognosis

- Good prognosis, less recurrent rate, remission is expected
  - Absence epilepsy (childhood & juvenile)
  - Benign partial epilepsy of childhood or benign rolandic epilepsy
  - Benign childhood epilepsy with occipital spikes
  - ……
- Good prognosis, with continuation of AED
  - Juvenile myoclonic epilepsy

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Types of Epilepsy of Poor Prognosis

- Infantile spasms & related epileptic syndrome
- Lennox-Gastaut syndrome
- Progressive myoclonic epilepsy
- Epilepsia partialis continua
- Epilepsy with multiple independent spikes
- Epilepsy with underlying structural or developmental defects
- Etc……

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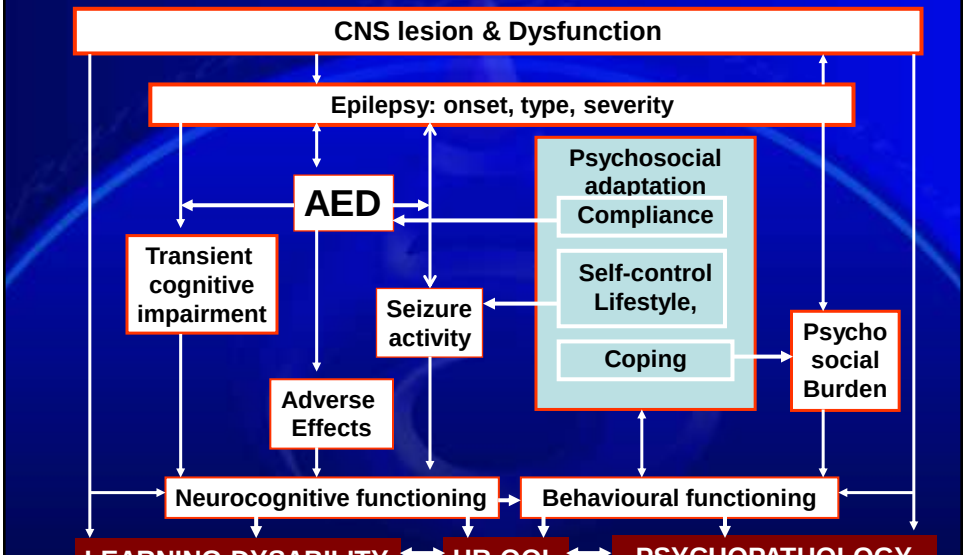
Conceptual Framework in Development of Mental Health Dysfunction in Children with Epilepsy



Adapt from: Noeker M, Brain & Development 2005

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Intellectual Functions in Epileptic Patients

- Lower IQ observed in
  - Younger age of onset
  - More frequent seizures
  - More frequent status epilepticus
  - Longer duration of seizures
  - Atypical absence seizures
  - Structural anomalies of brain

Farwell JR. Epilepsia 1985;26:395-400
Bourgeois BF, et al. Ann Neurol 1983; 14:438-444

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- Benign (adj.):
  - (of persons) = kind and gentle
  - (of soil, climate) = mild, favorable
  - (of a disease/tumor) = not dangerous

Advance Learner's Dictionary of Current English

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So called

- Localization-related epilepsy
  - Benign childhood epilepsy with centrotemporal spikes
  - Occipital lobe epilepsy
    - Panayiotopoulos type: Early onset benign childhood occipital epilepsy
    - Gastaut type: Late onset childhood occipital epilepsy
- Generalized epilepsy
  - Childhood & juvenile absence epilepsy
  - Juvenile myoclonic epilepsy

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Are they really benign?

- Localization-related epilepsy
  - Benign partial epilepsy of childhood or benign rolandic epilepsy
  - Benign childhood occipital lobe epilepsy
- Generalized epilepsy
  - Absence epilepsy
  - Juvenile myoclonic epilepsy

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Benign Childhood Epilepsy with Centrotemporal Spikes

- 10 – 20% of childhood epilepsy
- Unclear genetic basis of BCECTS
  - AD trait, Chromosome 15q14
  - Mutation of potassium channel gene KCNQ2
- Prognosis is favorable, spontaneous remission in majority before age of 13 years
- Frequent seizures: those with age of onset prior to 3 year

Benign Childhood Epilepsy with Centrotemporal Spikes

- Seizure
  - Typically infrequent
  - Nocturnal
  - Low incidence of status epilepticus
- Evolution to or relationship with
  - Landau-Kleffner syndrome
  - Epilepsy with continuous spike-wave during slow-wave sleep

Benign Childhood Epilepsy with Centrotemporal Spikes

- To treat or not to treat
- Usually single AED therapy with excellent response
- Spontaneous remission is expected
- Complete control in most patients

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Data in Thailand

Study at Ramathibodi Hospital

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BCECTS: Cognitive Dysfunction & Other Co-morbid

Author	Year	Country	Subjects	Results
Deonna T.	2000	Switzerland	22	Average IQ, school difficutly 36%, Delayed speech 18%, transient weak scores (verbal, visuospatial, memory): 36.
Yung AWY.	2000	USA	78	9%: IQ < 70, Borderline: 10%, behavioral problem 31%, LD 17%
Vinayan KP.	2005	India	50	Educational problems: 54% LD: 38%
Northcott E.	2005	Australia	42	Difficulties in memory & phonological processing skills
Connolly AM.	2006	Australia	30	Problem in higher competence Lower psychological scores (than control)
Riva D.	2007	Italy	24 (16 control)	Mild language deficits
Piccinelli P.	2008	Italy	20 (21 control)	Specific LD higher than control
Boatman DF	2008	USA	7 (7 control)	Impaired speech recognition 5/7
Danielsson J.	2009	Germany	25 (4-7 yrs) (25 control)	Verbal & nonverbal deficits, articulation, auditory memory, visual memory, language comphrehension)
Volkl-Kernstock S.	2009	Austria	20 (20 control)	Exhibition of attention problems & aggressive behavior
Ay Y.	2009	Turkey	25	Impaired visuomotor & reading ability Impaired attention to verbal stimuli
Goldberg-Stern H.	2010	Israel	36 (15 control)	Verbal functioning: lower than control
Lindgren A.	2004	Sweden	32 (25 control)	Transient cognitive impair (memory & learning of audioverbal material) cognitive flexibility & verbal fluency

BCECTS
Cognitive Dysfunction & Other Co-morbid

- Epileptiform discharge: Possible negative correlation
  - Absence of tangential dipole, high risk of educational problems **(Vinayan P. 2005)**
  - Spike/high frequency spike-wave in waking state had negative impact to cognitive function **(Wolf M. 2005, Riva D. 2007)**
  - Centrotemporal spikes affects auditory impairment **(Boatman DF. 2008)**
  - Epileptiform discharge during sleep may interfere with linguistic development **(Piccinelli P 2008)**
  - Epileptiform discharges relate to auditory discrimination & listening (Ay Y, 2009)
  - Result of pathological electrical discharges **(Goldberg-Stern H. 2010)**

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BCECTS
Cognitive Dysfunction & Other Co-morbid

- Epileptiform discharge:
  - May be transient/temporary, no correlation with EEG (Deonna T. 2000)
  - Improving of cognitive function when epileptiform discharges disappear (Baglietto MG. 2001)
  - No association between cognitive performance and side or bilaterality of epileptiform discharge (Danielsson J. 2009)
  - Cognitive function is independent to spike localization (Volkl-Kernstock S. 2009)
  - Recovery of LD after regression of epileptiform discharges at 5-yr follow-up (Lindgren A. 2010)

BCECTS
Relationship to LKS & CSWS

- Landau-Kleffner syndrome (LKS), continuous spike-and-waves during sleep syndrome (CSWS), and benign childhood epilepsy with centrotemporal spikes (BCECTS)
  - different entities
  - considered as part of a single continuous spectrum of disorders.

Rudolf G, et al. Epilepsia 2009 Aug;50 Suppl 7:25-8.

- BCECTS & LKS: Not possible to draw straightforward conclusions about the relationship between focal epileptic activity and the setting up of cognitive function

Rudolf G. Epilepsia 2006;47 Suppl 2:71-5.

Localization-related epilepsy

Benign childhood epilepsy with centrotemporal spikes

Benign Childhood Epilepsy with Occipital spikes

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Benign Childhood Epilepsy with Occipital Spikes

- Panayiotopoulous Syndrome
  - Mean age of onset < 5 years
  - Seizures:
    - Autonomic features are prominent (vomiting, pallor, miosis, hypersalivation, etc.)
    - Visual aura
    - Eye-starring or head/eye deviation with secondarily generalizde seizures
    - Nocturnal seizures

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Benign Childhood Epilepsy with Occipital Spikes

- Gastaut Syndrome
  - Mean age of onset: 8 - 9 years
  - Seizures:
    - Visual symptoms (blindness or visual hallucination)
    - Hemiclonic activity, versive movment, automatism
    - Migraine-like headache
    - Frequent seizures (> Panayiotopoulos syndrome)
    - Daytime seizures

Benign Childhood Epilepsy with Occipital Spikes

- Neuropsychological findings
  - Normal IQ
  - Learning disabilities
  - Linguistic & visual-perception dysfunctions
  - Attention and immediate recall deficits

Fois A. Epilepsia 1988;29:620-3.
Gulgonen S. Epilepsia 2000;41:405-11.
Germano E. Epilepsy Research 2005;64:137-150
Gokcay A. Seizure 2006;15:22-27

Author	Year	Country	Subjects	Age	Findings
Gulgonen S.	2000	Turkey	21 IOLE Control 21	6 - 14 years	Difference in attention, memory, & intellectual functions
Deonna T.	2000	Switzerland	19 BPERS, 3 BPEOS age 17 -54 years	4.5 - 5 years	1/3: weak visuo-spatial 1/3: visuo-construction
Germano E.	2005	Italy	22 BPEOS Control 28	10.1 +/- 3.3	Normal IQ Perceptive-visual attention, verbal & visual-spatial memory, Language tasks, reading & writing, Arithmetic
Chiolosi AM.	2006	Italy	11 IOLE, 11 ICEOP	3 - 17 years	Average IQ Abnormal visual perception (Apperceptive agnosis)
Barcia G.	2008	Italy	4 PS	5-15 years	Normal IQ, Abnromal visuospatial & visuomotor integration, Behavior disturbance
De Rose P.	2010	Italy	28 PS	4-15 years	Normal IQ, Abnromal visual assessment & visuoperceptual assessment
Specchio N.	2010	Italy	17 PS (control 19)	1.1 - 8.6 years	Normal IQ, significant difference in arithmetic, comprehension, & picture arrangement

Generalized epilepsy

Childhood & Juvenile absence epilepsy

Juvenile myoclonic epilepsy

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Absence Epilepsy

- CAE:
  - Remission rate about 80%
  - GTC seizures: about 40%
  - Persistence of seizures: more likely in those with GTC seizures.
  - Good prognostic signs:
    - Early onset of absence seizures,
    - Quick response to therapy
- JAE
  - Remission rate for JAE: less favorable than CAE.
  - Greater risk of GTC seizures (up to 80%) than CAE.
  - a high risk of GTC seizures.

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Absence Epilepsy
Cognitive Dysfunctions

- In patients with absence epilepsy
  - Evidence indicating general cognitive dysfunctions and visuospatial skills in patients with absence epilepsy
  - Memory disturbances with selective to nonverbal memory and delayed recall
  - Preserved verbal memory & language skill (*)

Pavone P, et al. Neurology 2001; 56: 1047-1051.
Study in Italian 16 children with absence epilepsy, aged 6 – 16 yrs (mean 9.2 yrs)

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Absence Epilepsy
Cognitive Dysfunctions

- Children with absence epilepsy, deficits in
  - Attention
  - Verbal learning and memory
  - Word fluency
  - Control of fine motor response
- Long-term risk of learning impairment, despite normal intelligence

Henkin Y, et al. DMCN 2005; 47: 126-132.
Study in Israeli children with 24 idiopathic generalized epilepsy (11 with absence seizures)
Well-controlled seizure, uniformly treated with VPA, normal intellectual & scholastic skills.

Absence Epilepsy
Cognitive Dysfunctions

- Positive effects of AED to children with absence epilepsy in attention, fine-motor fluency, and visual memory
- Longer duration of generalized 3-Hz spike-wave complexes: correlated with poor performance

Siren A, et al. Epilepsy Behav 2007;11:85-91.

- Absence was reported in only 0.4% of 8132 children with ADHD

Sinzig JK, von Gontard A. Klin Pediatrics 2005; 217: 230-3.

Absence Epilepsy
Cognitive Dysfunctions

- Cognitive changes in patients with childhood absence epilepsy in comparison with normal control
  - 25% with subtle cognitive deficits
  - 30% with linguistic difficulties
  - 61% with psychiatric problems including ADHD
- Spike-wave complexes can potentially cause significant brain & behavior dysfunctions

Caplan R, et al. Epilepsia 2008;49:1838-46.
Jacquin A. et al. Conf Proc IEEE Med Bio Soc 2007; 1928-31.

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Generalized epilepsy

Childhood & Juvenile absence epilepsy

Juvenile myoclonic epilepsy

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Juvenile Myoclonic Epilepsy

- Seizure: relatively easily controlled with AEDs (VPA, LTG, LEV, etc.)
- Life-long disorder and the majority needs treatment for years, even after prolonged remission
- Remission without medication was reported

Juvenile Myoclonic Epilepsy Long-term Outcomes

- Population-based study in Nova Scotia 24 pts, 25-year period demonstrated
  - **Seizure outcome:**
    - 6/24 seizure free, no medication (range 5-23 yrs.)
    - 3/24 myoclonic seizure, no medication (>18 yrs.)
    - 2/24 rare seizures
    - 12/24 Continue mediation (stop, recur, restart in 7)
    - 8/24 status epilepticus
    - 3/24 intractable epilepsy

Camfield C, Camfield P. Neurology 2009;73:1041-45

Juvenile Myoclonic Epilepsy
Long-term Outcomes

- Population-based study in Nova Scotia 24 pts, 25-year period demonstrated
  - **Social outcome:**
    - 65-77%: “very satisfied” with their health, work, friendships, social life
    - 87% : no educational problems
    - 69% : enough income to be self-sufficient
    - 74%: at least one major unfavorable social outcome (depression, anxiety, attention deficit)

Camfield C, Camfield P. Neurology 2009;73:1041-45

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Juvenile Myoclonic Epilepsy
Cognitive Impairment

- Impaired visual working memory
- Impaired frontal and visuospatial functions
- widespread cognitive dysfunction beyond frontal lobes
- Lower verbal learning than control
- Impaired verbal fluency

Devinsky O, et al. Neurology 1997;10:243-6.
Savic I, et al. Epilepsia 2000;41:290-6.
Hommet C. et al. Neruosci Biobehav 2006;30:85-96.
Kim SY, et al. J Clin Neurology 2007;3:86-92.
Piazzini A, et al. 2008;49: 657-662.
Iqbal N, et al. 2009;14: 516-21.

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Author	Year	Country	Subjects	Findings	Remarks
Sonmez F.	2004	Turkey	35 Pt, age 16-35 years	Executive processing and visuospatial dysfunctions	Less successful copying, drawing More repetitive learn for verbal memory process Longer time in reading black & white and colored cards,
Pascalicchio TF.	2007	Brazil	50 pts, age 17 -54 years	Widespread cognitive dysfunction beyond frontal lobes	Degree of cognitive impairment: correlated to duration of epilepsy (in years)
Kim SY.	2007	Korea	27 pts, & control age 16 - 29 years	Lower verbal learning, impaired verbal fluency Attention deficit, normal intellectual & mood	Deficits were not correlated with age, sex, education level, AED
Piazzubu A.	2008	Italy	50 pts, JME, TLE, FLE, age 18 - 60 yrs	Severe impairment of administrative tasks reflecting frontal dysfunction similar to FLE & TLE pts.	Deficits in planning, concepts formation, elaborating strategies for the attainment of immediate or future goals, verbal fluidity
Iqbal N.	2009	English	8 pts, compare with sibling & control	JME pts had significant differences on phonamic & semantic fluency measurement	No evidence from simultaneous EEG recording during the test demonstrates subclinical discharge reduced test performance

Juvenile Myoclonic Epilepsy Cognitive Impairment

- Decreased metabolism in prefrontal and frontal lobe
- High frequency of interictal epileptiform discharge may relate to impaired digit span performance
- Microdysgenesis or disorganization of cortex

Swartz ER, et al.Neurology 1996;47:1203-12.
Devinsky O, et al. Neurology 1997;10:243-6.
Savic I, et al. Epilepsia 2000;41:290-6.
Lavandier N, et al. Rev Neurol 2002;158:164-5.
Hommet C. et al. Neruosci Biobehav 2006;30:85-96.
Kim SY, et al. J Clin Neurology 2007;3:86-92.
Piazzini A, et al. 2008;49: 657-662.

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Benign Epilepsy
Take home message

- Psychological and cognitive dysfunctions are evidence
- Though, most of dysfunctions are transient, awareness of these co-morbidities is crucial for proper care of these patients while remission is not achieved.
- In addition, there are subgroups or variants of which, the prognosis is not straight forward as the typical one.

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