Natural Course and Prognosis of Epilepsy

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Introduction

- Prognosis of epilepsy generally means probability of being seizure-free
  - after starting treatment
  - during treatment
  - after drug withdrawal
- Psychosocial outcomes of epilepsy is being paid attention on. (not including in my talk today)
- Prognosis of untreated epilepsy
  - There are only a few reports
  - Mostly from resource-poor countries

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Methodologic issues

- Prognosis of epilepsy depends on
  - characteristics of patients
  - case definition
  - spectrum of severity of epilepsy
  - duration of follow-up
  - choice of prognostic predictors
  - choice of treatments

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Methodologic issues

- Prognosis of epilepsy depends on
  - characteristics of patients

e.g. patients with normal brain imaging

e.g. idiopathic generalized epilepsy

e.g. newly diagnosed patients versus

e.g. 2-year follow up versus

e.g. normal EEG versus

e.g. medication Rx versus surgical Rx in mesial temporal sclerosis

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Ideal design of study on prognosis of epilepsy

- Well-defined inclusion criteria
- Homogenous definition on prognostic predictors and outcome measurements
- Adequate duration of follow-up and proper statistical methods to adjust for those lost to follow-up or limited periods of follow-up

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Overall prognosis of epilepsy

- Incidence of epilepsy in health resource-poor countries are higher than that in industrialized countries
  - 30-60 per 100,000 Vs 70 per 100,000
- However the prevalence of epilepsy in health resource-poor countries are broadly similar to that in industrialized countries.
- Prevalence of active epilepsy are between 4-10 per 1,000.

Beghi E, Sander JW. The natural history and prognosis of epilepsy. In: Engel J. Pedley TA, eds. Epilepsy: A comprehensive textbook. 2nd ed. LWW; 2008: 65-70.

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Overall prognosis of epilepsy

- The increased mortality of epilepsy in resource-poor countries explains only part or the difference between incidence and prevalence.
- The most likely explanation for the similar prevalence rates between the resource-poor and the resource-rich countries is
  - spontaneous remission in some patients
- Therefore, overall prognosis of epilepsy is favorable in the majority of patients.

Beghi E, Sander JW. The natural history and prognosis of epilepsy. In: Engel J. Pedley TA, eds. Epilepsy: A comprehensive textbook. 2nd ed. LWW; 2008: 65-70.

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Prognosis after the first unprovoked seizures

- The reported risk of relapse after the 1st unprovoked seizure range from 14-68%.
- The reported relapse rate at 2 years are 21-69%.
- The reported relapse rate at 5 years are 34->71%.
- Population-based studies reported relapse rates
  - at 1 year   = 36-37%
  - at 2 years = 43-45%

Beghi E, Sander JW. The natural history and prognosis of epilepsy. In: Engel J. Pedley TA, eds. Epilepsy: A comprehensive textbook. 2nd ed. LWW; 2008: 65-70.

Prognosis after the first unprovoked seizures

- In a systematic review from 16 reports
  - The average overall recurrence risk is 51% (95% CI, 49-53%).
- The probability of relapse decrease with time.
  - About 50% of recurrences occur within the initial 6 months
  - About 76-96% of recurrences occur within the 2 years

Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology.1991;41(7):965-972.

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Relapse risk factors of a 1st unprovoked seizure

- 2 most consistent predictors
  - Brain pathology
  - Abnormal EEG (epileptiform and/or slow activity)

Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology.1991;41(7):965-972.

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Treatment, risk of recurrence, long-term prognosis of early epilepsy and 1st seizure

The Mess study

- Large pragmatic randomized European trial
- Comparing immediate and deferred AED for early epilepsy and 1st seizure
- Total 1,443 patients aged at least 1 month who and whose doctors were uncertain on starting AED were randomized.

Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005;365(9476):2007-2013.

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	Immediate AED	Deferred AED	Stat
Randomized No.	722	721	
1st seizure	404	408	
Time to the first relapse	prolonged		RR 1.5; 95%CI, 1.2-1.8
Seizure recurrence at 2-yr follow-up	32%	39%	
2-yr remission at 2 yr	64%	52%	p = 0.023
2-yr remission at 5 yr	92%	92%	
2-yr remission at 8 yr	95%	96%	

Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005;365(9476):2007-2013.

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Treatment, risk of recurrence, long-term prognosis of early epilepsy and 1st seizure

- Immediate AED Rx of 1st seizure or early epilepsy
  - It seems to reduce the risk of short-term relapse.
  - Long term prognosis is substantially unaffected.
- The comparative effects of immediate AED for 1st seizure and deferred AED until relapse on the chance of long-term remission after AED discontinuation have not yet been assessed.

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Prognosis of untreated epilepsy

- The prognosis of untreated epilepsy come from resource-poor countries.
- A population-based study in Ecuador[1]
  - Cumulative annual incidence rate 190 per 100,000
  - Prevalence rate of active of epilepsy 7 per 1,000
  - Imply a remission rate of at least 50%

Placencia M, Shorvon SD, Paredes V, et al. Epileptic seizures in an Andean region of Ecuador. Incidence and prevalence and regional variation. Brain. 1992;115 :771-782.

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Prognosis of untreated epilepsy

- A small study in Finland conducted in untreated patients with epilepsy found the probability of remission to be 42% by 10 years after seizure onset

Keranen T, Riekkinen Pj. Remission of seizures in untreated epilepsy. BMJ. 1993;307(6902) :483.

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Prognosis of newly diagnosed epilepsy

- Population-based studies on the long-term prognosis of treated (newly diagnosed) epilepsy report cumulative 5-year remission rate
  - at 10 years = 58-65%[1,2]
  - at 20 years = 70%[1]
- The 5-year remission rate at 10 years is 61% in adult patients.[3]

1. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia.1979;20(6):729-737.
2. Annegers JF, Shirts SB, Hauser WA, et al. Risk of recurrence after an initial unprovoked seizure. Epilepsia.1986;27(1):43-50.
3.Lindsten H, Stenlund H, Forsgren L. Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure. Epilepsia. 2001;42(8):1025-1030.

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Prognosis of newly diagnosed epilepsy

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Overall, epilepsy will be well controlled approximately 60-70%.

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2. Annegers JF, Shirts SB, Hauser WA, et al. Risk of recurrence after an initial unprovoked seizure. Epilepsia.1986;27(1):43-50.
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Principal prognostic predictors

- Prognostic predictor of seizure remission
  - Etiology of epilepsy is the strongest predictor.
    - Idiopathic epilepsy has better chance of remission than cryptogenic/symptomatic epilepsy.
  - Absence of EEG epileptiform abnormalities
- Age and sex are not prognostic predictor of seizure remission.

Beghi E, Sander JW. The natural history and prognosis of epilepsy. In: Engel J. Pedley TA, eds. Epilepsy: A comprehensive textbook. 2nd ed. LWW; 2008: 65-70.

Principal prognostic predictors

- Early predictors of seizure intractability
    - Etiology of epilepsy
    - High initial seizure frequency
    - Focal EEG slowing

Berg AT, Shinnar S, Levy SR, et al. Early development of intractable epilepsy inchildren: a prospective study. Neurology.2001;56(11):1445-1452

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Prognosis of epilepsy and epilepsy syndromes

- Epilepsy and epilepsy syndromes can be classified into 4 prognostic groups
    - Excellent prognosis (20-30%)
        - High probability of spontaneous remission
    - Good prognosis (30-40%)
        - Easy pharmacologic control and possibility of spontaneous remission
    - AED-dependent prognosis (10-20%)
        - Tend to relapse after AED withdrawal
    - Guarded prognosis (20%)
        - Tend to intractable to AEDs

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Epilepsy and epilepsy syndrome with excellent prognosis

- High probability of spontaneous remission
- Including
    - Neonatal seizure
    - Benign partial epilepsies
    - Benign myoclonic epilepsy in infancy
    - Epilepsies provoked by specific modes of activation

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Epilepsy and epilepsy syndrome with good prognosis

- Easy pharmacologic control and possibility of spontaneous remission
- Including
    - Infantile absence epilepsy
    - Epilepsies with generalized-tonic-clonic seizures secondary to specific conditions
    - Some partial epilepsies

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Epilepsy and epilepsy syndrome with AED-dependent prognosis

- May respond to AED
- Tend to relapse after AED withdrawal
- Include
    - Juvenile myoclonic epilepsy
    - Most partial epilepies (symptomatic or cryptogenic)

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Epilepsy and epilepsy syndrome with guarded prognosis

- Seizures tend to recur despite intensive treatment
- Include
    - Epilepsies ass. with congenital neurologic defects
    - Progressive neurologic disorders
    - Some symptomatic or cryptogenic partial epilepsies

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Antiepileptic drugs and seizure outcome

- AEDs do not alter long-term epilepsy outcome.
- There are no reports on the comparative efficacy of old and new AEDs on the long-term outcome of epilepsy.
- There is no evidence to suggest that the newer medications are more efficacious.
- The majority of seizure-free patients required only a moderate daily dose of AED.

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Prognosis of epilepsy after AED withdrawal

- Specchio LM and Beghi E reviewed 28 studies,
  - total 4,615 patients
  - most patients had at least 2 years seizure remission
  - Proportion of seizure recurrence during or after AED discontinuation = 12-66%

Specchio LM, Beghi E. Should antiepileptic drugs be withdrawan in seizure-free patients? CNS drugs. 2004;18(4):201-212.

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Prognosis of epilepsy after AED withdrawal

Cumulative probability of remaining seizure-free	Children	Adults
at 1 year	66-96%	39-74%
at 2 years	61-91%	35-57%

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Prognosis of epilepsy after AED withdrawal

- The relapse rate
  - Highest in the initial 12 months
    - especially initial 6 months
  - Tend to decrease with time
- A meta-analysis of 25 studies by Berg AT and Shinnar S in 1994, the pooled relapse rate was
  - at 1 year = 25% (95%CI, 21-30%)
  - at 2 years = 29% (95%CI, 24-34%)

Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. Neurology. 1994;44(4) :601-608.

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Prognosis of epilepsy after AED withdrawal

- A randomized trial on the effects of AED withdrawal on seizure relapse
  - Relapse by 2 years:
    - on AED vs. off AED = 22% : 41%
  - The difference of relapse rate was
    - maximal between initial 1 and 2 years
    - decrease thereafter
  - After 2 years, risk of relapse was the same in both on AED and off AED gr.

Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet. 1991;337(8751):1175-1180.

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Prognosis of epilepsy after AED withdrawal

- The risk of seizure recurrence was similar in both patients who relapsed after off AEDs and those during on AEDs.

Chadwick D, Taylor J, Johnson T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. The MRC Antiepileptic Drug Withdrawal Study Group. Epilepsia. 1996;37(11):1043-1050.

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Factors predicting seizure relapse after AED withdrawal

- In the Medical Research Council AED withdrawal study, predictors of relapse are
  - Seizure types
    - Partial seizure
    - Primarily or secondarily generalized tonic-clonic seizure
    - Myoclonic seizure
  - Use of more than one AED
  - Seizures after treatment start
  - Shorter seizure-free period

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Factors predicting seizure relapse after AED withdrawal

- A meta-analysis of 25 studies by Berg AT and Shinnar S in 1994,
  - Adolescence onset had 1.34-fold increased risk of relapse (95%CI, 1.00-1.81) vs. adult onset
  - Remote symptomatic epilepsy had 1.55-fold increased risk of relapse (95%CI, 1.21-1.98)
  - Abnormal EEG prior to drug withdrawal ass with 1.45-fold increased risk of relapse (95%CI, 1.18-1.79)
  - 2-yr vs. 4-yr seizure-free interval was similar.

Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. Neurology. 1994;44(4) :601-608.

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Factors predicting seizure relapse after AED withdrawal

- A RCT comparing 6-week taper vs. 9-month taper after 2 year seizure remission in children with epilepsy showed no difference in recurrence risk at 2 years

Tennison m, Greenwood R, Lewis D, et al. Discontinuation of antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. N Engl J Med. 1994;330(20):1407-1410.

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Thank You !