C2C: Seizures & Epilepsy ECHO

Overview of Seizures and Epilepsies

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Key Topics

- Seizures and Epilepsy
- Evaluation of Seizures
- Febrile Seizures
- History and Examination
- When to Refer

Survey Question 1

An 18 y/o female, school student, comes for a follow-up visit. She had an event consistent with generalized tonic-clonic seizure 1 week ago, witnessed by a classmate, who reported that the seizure started suddenly with stiffening of whole body, followed by jerking movements of both arms and legs. The patient does not report any warning symptoms prior to the seizure. She was treated in the ER and sent home on maintenance dose of levetiracetam (LEV). A routine (30 min) EEG and head CT, obtained in the ER, were normal. The patient states that the week prior to the seizure, she usually slept no more than 2 hours/night due to school assignments. There is no family h/o seizures. Neurologic exam is normal.

Which of the following is the next best step in the management?

(1) Wean off Keppra

(2) Obtain brain MRI

(3) Obtain prolonged EEG, brain MRI, switch to phenytoin, and educate about seizure precautions

(4) Obtain additional history, prolonged EEG, and educate about seizure precautions

Survey Question 2

A 4 y/o boy is brought to the office for evaluation of events concerning for seizures, noted since last 3-4 months. The events typically occur in school and have been witnessed by the teacher. The patient will often start to cry, his breathing may become deep and/or fast. This may continue on and off for a few minutes. Sometimes there is low amplitude shaking of both the arms. The patient appears to remain aware throughout but may not respond to the teacher's voice. There have been several concerns about his bullying in the school since last 4-5 months. There is h/o epilepsy in maternal GM. He is typically developing, and has a normal neurological exam.

Which of the following is the next best step?

(1) Make a presumptive dx of epilepsy and start on carbamazepine

(2) Obtain a routine EEG and brain MRI

(3) Request parents and/or teacher to videotape the events and obtain a routine EEG

(4) Reassure the parents that these are not seizures and no further action is needed

UNDERSTANDING SEIZURES: THE BASICS

What is a Seizure/Convulsion?

- A sudden stereotyped episode with change in motor activity, sensation, behavior, and/or consciousness
  - Due to abnormal hypersynchronous electrical discharge(s) in the brain
- Convulsions vs. Seizures
  - Several types of seizures have symptoms other than shaking

Source: http://www.nlm.nih.gov/medlineplus/ency/article/003200.htm

Seizure: Symptoms

Symptoms often depend upon the area in the brain where the seizure starts and how the seizure propagates

- Behavioral arrest
- Changes in behavior including mood changes
- Bitter/metallic taste
- Purposeless movements such as picking at one's clothes (automatisms)
- Abnormal eye movements, eye deviation
- Drooling, frothing at the mouth
- Rhythmic twitching or jerking of limbs or face or the entire body
- Staring
- Eye lid fluttering
- Sudden fall(s)
- Loss of tone or stiffening of the extremities
- Teeth clenching
- Temporary stop in breathing

https://medlineplus.gov/ency/article/003200.htm

Seizures: Causes

Seizures can be

- Provoked: seizure with an acute antecedent cause, such as:
  - CNS infection (meningitis, encephalitis)
  - Trauma
  - Metabolic abnormality (abnormal level of glucose, sodium)
  - Toxic exposure (drugs, alchohol)
  - Fever
- Unprovoked: no immediate provoking factor

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Source:
Joshi and Shellhaas 2014

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Seizures: Causes

- A cause is identifiable in <20% of children with seizures
- Other causes of seizures include:
  - Brain malformations
  - Perinatal hypoxia/ischemia
  - Genetic disorders
  - Disorders of metabolism
  - Traumatic or previous infectious injury of the brain
  - Neoplasms
- Neurodevelopmental abnormalities make it more likely a cause will be identified or may already have been determined before seizure onset.

https://pediatriccare.solutions.aap.org/content.aspx?resultClick=1&gbosid=165567

Seizures: Epidemiology

- Prevalence
  - Seizures occur in approximately 1% of all children up to the age of 14 years.
  - Greatest in first year of life (~120 cases per 100,000 population).
  - Thereafter, 40-50 cases per 100,000 population until puberty.
  - ~10 cases per 100,000 population in the early and mid teens
  - ~15% of children who have epilepsy have intractable seizures
    - ~50% of these may be appropriate candidates for epilepsy surgery.

https://pediatriccare.solutions.aap.org/content.aspx?resultClick=1&gbosid=165567

FEBRILE SEIZURES

Febrile Seizures

- A seizure that occurs in association with a fever (temperature at or above 100.4F or 38C by any method)
- Very common in children (3-4%)
- Age of onset
  - Age 6 months to 5 years (median 18-22 months)
- No evidence of a CNS infection, or acute neurologic illness
- Usually occurs in an otherwise normal child
- There may/may not be a family history of febrile seizures/epilepsy

http://pediatrics.aappublications.org/content/pediatrics/127/2/389.full.pdf

http://pediatriccare.solutions.aap.org/chapter.aspx?sectionId=56754849&bookId=1017&resultClick=1

Febrile Seizures

- Simple Febrile seizures are generalized tonic-clonic convulsions that last less than 15 minutes and do not recur within 24 hours.
- Complex febrile seizures are less common and are focal or prolonged beyone 15 minutes or recur within 24 hours. These account for about 25% of febrile seizures.

Febrile Seizures

- Triggered by any illness that causes fever, most frequently by otitis media and upper respiratory tract infections, roseola, gastroenteritis.
- A febrile seizure can be the first sign of a febrile illness.
- 1/3 of children who have a febrile seizure will have another one with another febrile illness.
- The younger the child is at the time of the first episode, the greater the risk is of recurrence.
- Approximately 50% of the recurrences occur within 6 months of the initial seizure; 75% occur within 1 year.

Febrile Seizures: Evaluation

- Thorough history and examination
  - Aimed at determining the cause of fever
- Diagnostic studies: Are they needed?
- Tests that are considered include:
  - Lumbar puncture
  - EEG
  - Neuroimaging
  - Other blood tests

Source: Baumann RJ, Duffner PK. Pediatr Neurol. 2000

Febrile Seizures: Evaluation

Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

Subcommittee on Febrile Seizures

Pediatrics 2011;127;389

"In general, a *simple* febrile seizure does not usually require further evaluation, specifically EEG, blood studies, or neuroimaging."

Clinical Practice Guideline

Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

- A lumbar puncture (LP) should be performed in any child who presents with a seizure and a fever and has meningeal signs and symptoms (e.g., neck stiffness, Kernig and/or Brudzinski signs) or in any child whose history or examination suggest the presence of meningitis or intracranial infection.

Clinical Practice Guideline

Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

- In any infant between 6 and 12 months of age who presents with a seizure and fever, a LP is an option when the child is considered deficient in Haemophilus influenza type b (Hib) or Streptococcus pneumonia immunizations (i.e., has not received scheduled immunizations as recommended) or when immunization status cannot be determined because of an increased risk of bacterial meningitis

Clinical Practice Guideline

Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

- A LP is an option in the child who presents with a seizure and fever and is pretreated with antibiotics, because antibiotic treatment can mask the signs and symptoms of meningitis.

http://pediatrics.aappublications.org/content/pediatrics/127/2/389.full.pdf

Clinical Practice Guideline

Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

- An electroencephalogram (EEG) should not be performed in the evaluation of a neurologically healthy child with a simple febrile seizure.
- The following tests should not be performed routinely for the sole purpose of identifying the cause of a simple febrile seizure: measurement of serum electrolytes, calcium, phosphorus, magnesium, or blood glucose or complete blood cell count.
- Neuroimaging should not be performed in the routine evaluation of the child with a simple febrile seizure.

Febrile Seizures: Management

Febrile Seizures: Clinical Practice Guideline for the Long-term Management of the Child With Simple Febrile Seizures

Subcommittee on Febrile Seizures

Pediatrics 2008;121;1281

Febrile Seizures

- Prognosis: excellent, except:
  - 30-50% risk of recurrence
  - Double the risk of epilepsy, 1% ➡ 2%

Additional Discussion:
Risk factors for later development of epilepsy

Febrile Seizures: Recurrence

- Risk factors (after 1 simple febrile seizure):
  - Age <18 months
  - Family history of febrile seizures (1st degree relative)
  - Low degree of fever at the time of the seizure
  - Short duration of illness before occurrence of seizure
- Overall Recurrence Risk = 32% over the next 2 years.
- Recurrence risk (based on above risk factors):
  - NO risk factors: 4%
  - 1 risk factor: 23%
  - 2 risk factors: 32%
  - 3 risk factors: 62%
  - 4 risk factors: 76%

Source: Berg AT, et al. Arch Pediatr Adolesc Med 1997

Treatment

- Treatment of seizure
  - Often the seizure has stopped by the time the child is brought in for evaluation.
  - If the seizure continues, then lorazepam or diazepam should be administered

- Treatment of fever
  - The temperature should be brought down by using rectal antipyretics, removing blankets and clothing, and sponging
  - Once the seizure is controlled, evaluation is directed toward finding the cause of the fever.

https://pediatriccare.solutions.aap.org/book.aspx?bookid=1626

Treatment

- Family education that addresses the benign nature of the seizures, the use of antipyretics, and first aid for seizures.
- Oral diazepam (0.33 mg/kg body weight administered every 8 hours during febrile illness) reduces the risk of recurrent febrile seizures: discuss

https://pediatriccare.solutions.aap.org/book.aspx?bookid=1626

Treatment

- Prophylactic treatment with anticonvulsant agents could be considered if neurologic development is abnormal, it is a complex febrile seizure, or the child is younger than 1 year.
- Valproate and phenobarbital appear to be effective in prophylaxis; phenytoin and carbamazepine do not prevent recurrences. The adverse effects of anticonvulsant therapy must be weighed against the possible benefits.
- No evidence has been found that prophylactic treatment reduces the risk of subsequent epilepsy.

EPILEPSY

If seizures continue repeatedly after the underlying problem is treated, the condition is called epilepsy

What is Epilepsy?

- Epilepsy is defined by recurrent unprovoked seizures.
- Lifetime prevalence of epilepsy to be 10.2/1000 or 1% (Russ et al, Pediatrics 2012).
- Approximately 1 in 26 people will develop epilepsy at some point in their lives.
- Epilepsy affects an estimated 2.2 million people in the United States.

ILAE Operational Definition of Epilepsy

Table 2. Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Table 1. Conceptual definition of seizure and epilepsy – 2005 report

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

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

Fisher et al. Epilepsia 2014

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Epilepsy

- Living with epilepsy is about more than just seizures; it is often defined in practical terms, such as challenges, uncertainties, and limitations in school, social situations, employment, driving, and independent living. People with epilepsy are also faced with health and community services that are fragmented, uncoordinated, and difficult to obtain (IOM Report, 2012)

What is Epilepsy?

- Epilepsy is more than seizures, it is a complex disease with several neurological and psychiatric co-morbidities:
  - Depression
  - ADHD
  - Anxiety
  - Conduct Problems (Russ et al, Pediatrics 2012)
  - Developmental delay
  - Autism/Autism Spectrum disorder

TABLE 1 Sociodemographic Correlates of Lifetime Epilepsy /Seizure Disorder

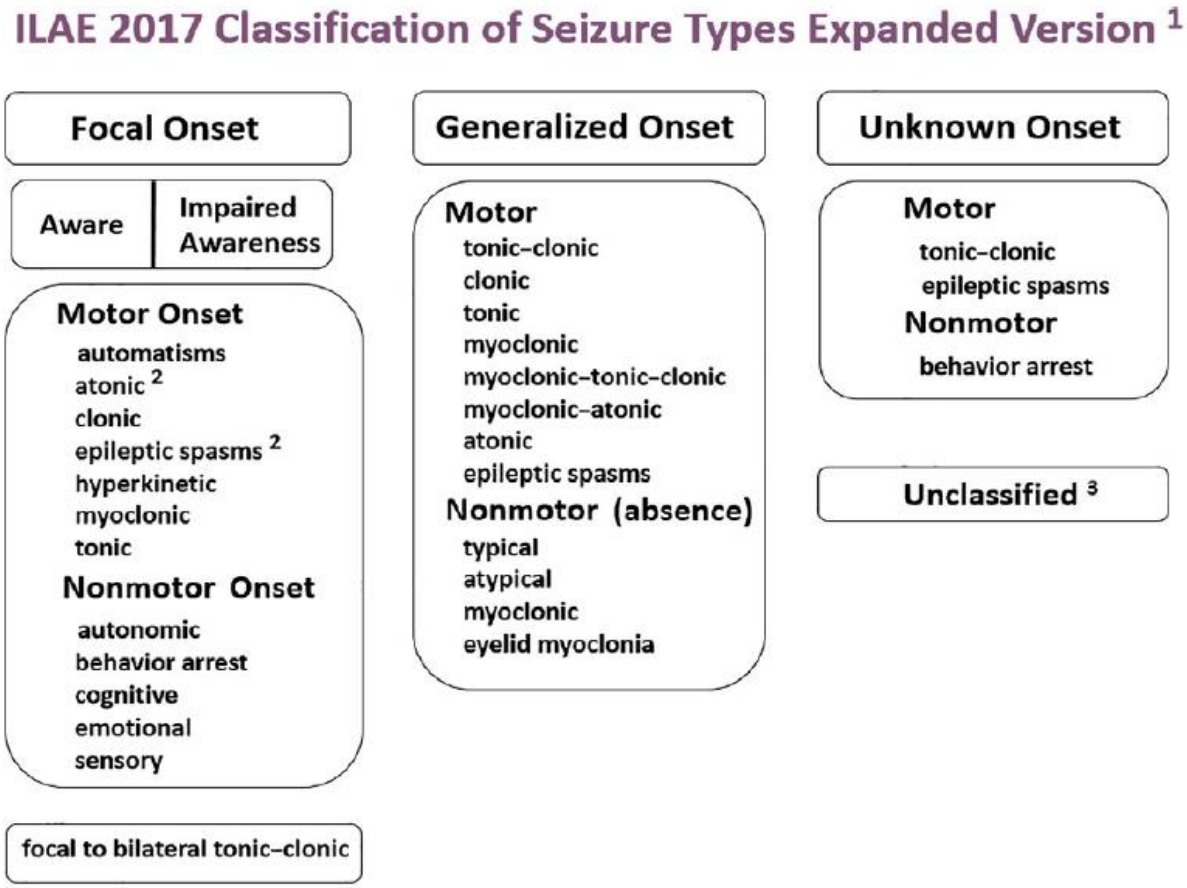
	Child Ever Diagnosed with Epilepsy/Seizure Disorder					
	No. in Sample (Unweighted)	No. Ever Diagnosed (Unweighted)	Weighted Prevalence per 1000	95% CI per 1000	Adjusted RR	95% CI
Total	91 605	977	10.2	8.7–11.8		
Former diagnosis		451	3.9	3.3–4.6		
Current diagnosis		526	6.3	4.9–7.8		
Household income						
<100% FPL	10 956	170	12.8	9.6–17.1	1.95	1.16–3.27
100% –199% FPL	15 575	226	12.5	9.8–15.9	1.79	1.20–2.65
200% –299% FPL	16 531	183	12.4	7.6–20.2	1.51	0.80–2.85
300% –399% FPL	14 215	111	5.9	4.3–8.1	0.78	0.51–1.17
400% FPL or greater	34 328	287	7.7	6.0–10.0	base	
Family structure						
Two biological/ adoptive parents	70 595	669	9.1	7.4–11.2	base	
Single mother	14 722	217	13.6	10.7–17.2	1.22	0.86–1.73
Other	5741	86	13.6	9.8–18.7	1.20	0.80–1.80
Race/Ethnicity						
White	61 352	633	10.9	8.8–13.5	base	
African American	8869	108	10.6	7.8–14.3	0.72	0.51–1.03
Hispanic	11 520	121	8.9	6.2–12.9	0.68	0.43–1.06
Multiracial/Other	8320	95	8.2	4.9–13.4	0.75	0.44–1.27
Highest parent education						
HS diploma	20 811	309	11.7	9.6–14.1	1.03	0.73–1.45
More than HS	69 703	658	9.5	7.7–11.8	base	
Child age, y						
0–5	27 555	204	6.3	4.9–8.3	base	
6–11	27 781	303	10.3	8.2–12.8	1.62	1.13–2.31
12–17	36 269	470	14.0	10.8–18.2	2.26	1.54–3.33
Child gender						
Male	47 513	508	11.8	9.4–14.9	1.38	1.03–1.84
Female	43 983	469	8.6	7.2–10.3	base	

FPL, federal poverty level.

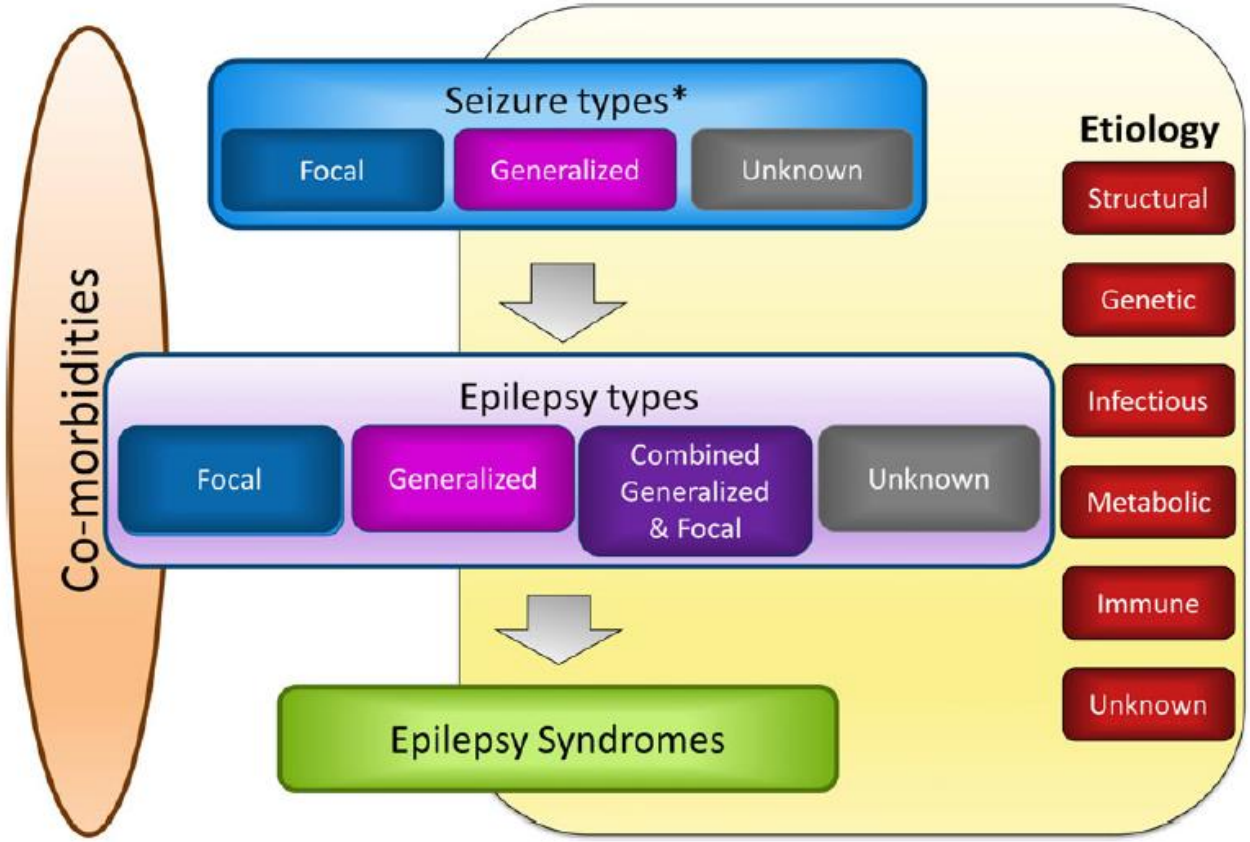
Categorizing Epilepsy Syndromes

- Clusters of signs and symptoms
  - Age of onset, severity
  - Diurnal or nocturnal occurrence
  - Clinical course
  - Associated neurologic dysfunction
  - Inheritance

ILAE classification of seizures



ILAE classification of epilepsies



Important Aspects of the History and Exam

- Primary care physician is usually the first point of contact after a child has a seizure (Basco et al, Pediatrics 2013)
- If the patient is not actively seizing at the time of evaluation
  - Obtain a clear history of the event, preferably in person from a witness, so as to be able to distinguish the event from other non-epileptic events (to be discussed separately).

https://www.epilepsy.com/learn/professionals/diagnosis-treatment/emergency-department-care/first-or-unknown-seizure-history

Past and Recent Medical History

- Known risk factors
  - Pre/peri/post-natal complications
  - Head trauma
  - CNS infections
  - Febrile Seizures
  - Other medical conditions
- Recent symptoms (illness, head injury, lack of sleep, dehydration)
- Developmental history
- Medications/toxin exposures (EtOH, illicits, Rx meds, etc.)
- Family history
  - Febrile seizures or epilepsy, 1st and 2nd degree relatives

Source: Fenton, 2014

Seizure-Specific History

- Context of event(s)
  - Circumstances under which the events occur
  - Timing and circadian distribution
  - Position (lying, sitting, standing, transitions)
  - Associated activities at the time of the event (at rest, during exercise)
  - Triggering factors (crying, fever, etc.)
  - Facilitating factors (dehydration, illness, alcohol/illicit drug consumption, sleep deprivation)
- Detailed description of all event(s)
  - Was the onset witnessed
  - Description from start to end, including the aura and postictal effects, until recovery to normal.

Seizure-Specific History

- Difficulty in diagnosis and potential misdiagnosis can result from failure to obtain a detailed description of the event
  - Not enough time to spend taking detailed history
  - Inexact historian
  - Witness not available
  - Onset not witnessed
- Importance of documentation of detailed history to help facilitate care coordination between primary care and specialists.

Source: Fenton, 2014

Seizure-Specific History: Staring

- Spells noted in multiple environments (absence)
- Spells interrupt activities (absence) or have postictal manifestations (focal)
- Spells don’t stop with physical touch
- Spells precipitated by hyperventilation during exam

Source: Fenton, 2014

Seizure-Specific History

- Was there a warning right before the convulsion (behavioral arrest, affective change)?
- Did the head/eyes deviate upward or to one side?
- Did the movements start unilaterally or bilaterally?
- How did the seizure progress?
- How long did the seizure last?
- What was the child like immediately after and how long to recover to baseline?

Source: Fenton, 2014

Neurologic Examination

- A screening neurologic exam is most appropriate, assessing for multiple signs indicative of neurologic injury.
- Cranial nerves: Pupil reactivity, nystagmus, facial symmetry/strength, palate elevation, tongue protrusion.
- Motor: muscle bulk, tone, and strength (assess for asymmetries), reflexes, Babinski response
- Coordination: finger to nose movements (assess for focal tremors)
- Gait: Look for ataxia, circumduction.

Source: Fenton, 2014

Condition-Specific Assessment

- CNS infection
  - Fever, headache, prolonged seizure, prolonged postictal state
  - Stiff neck
- Head trauma
  - History, external evidence, focal deficit
- Brain tumor
  - Headache, focal seizure, focal deficits

Source: Fenton, 2014

Condition-Specific Assessment

- Genetic syndromes and brain malformations
  - Developmental delay, Dysmorphism
- Cerebral hemorrhage
  - Trauma, family history of cerebral cavernous malformations, focal seizures, focal deficits
- Neurocutaneous disorders
  - Birthmarks (hypopigmented macules, café au lait spots, etc.)

Source: Fenton, 2014

Recap: Key Areas of Focus

- Seizure-specific history
  - Assure the event(s) is/are seizures
  - Categorize seizure type
  - Suggest possible etiology
- Past and recent medical history
  - Identify risk factors
- General physical examination
  - Looking for a symptomatic etiology
- Neurological examination
  - Looking for evidence of a symptomatic etiology

Source: Fenton, 2014

Questions About Seizures?

1. Are the events Seizures?
   - Detailed description of events
   - EEG
2. What type of seizures are they?
   - Detailed description of events
   - EEG
3. What is the cause of the seizures?
   - Detailed description of events
   - Past and recent medical history
   - Family history
   - Lab Studies
4. What is the likelihood of recurrence?
   - Detailed description of events
   - Past and recent medical history
   - Family history
   - EEG and other lab studies
5. What treatment should be given?
   - Safety precautions
   - Rescue medication
   - Preventive medication

Source: Fenton, 2014

Partnering with Parents After a Seizure

- Parents and patients may have many fears and need reassurance.
  - Explain the terms *epilepsy* or *seizure disorder.*
  - Help parents understand that diagnosis of epilepsy alone does not mean that the child has intellectual disability or a psychiatric disorder, but may co-occur with epilepsy
  - Give the guidelines on what to do when child has a seizure, including positioning on the side and putting nothing in the mouth.
  - Emphasize to parents that death from a seizure is rare.
  - Educate parent/family over time to help process all information during high stress time of new diagnosis

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Addressing Parents After a Seizure

- Discuss activities of patients with seizures.
  - Activities should be restricted as little as possible.
  - A child with a seizure disorder should not swim alone or go bike riding without a helmet (as for all children).
  - Contact sports are permissible when epilepsy is controlled.
  - The decision about climbing up to certain heights should be based on how well the child's seizures are controlled. Extreme heights, such as rock climbing, should always have a belay.
  - Older children who are not supervised when bathing should be encouraged to take showers rather than baths to minimize risk of drowning if a seizure occurs.

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Diagnostic delays in children with early onset epilepsy: Impact, reasons, and opportunities to improve care

*Anne T. Berg, †Tobias Loddenkemper, and ‡§Christine B. Baca

Epilepsia, 55(1):123–132, 2014
doi: 10.1111/epi.12479

- Connecticut Study of Childhood epilepsy first diagnosed 1993-1997
  - Limited study to children with onset <3 years of age
  - 17 pediatric neurologists serving about 500,000 children
- Assessed time from second seizure to diagnosis of epilepsy
- Regarded >1 month as a delay in diagnosis
- 1-4 months, 4-12 months, >12 months
- Looked for reasons for diagnostic delay; Correlated diagnostic delay with outcome
- Diagnostic delays occurred in 41% (21% at 1-4 months) (7% at 4-12 months) (13% at >12 months)
- Diagnostic delay less likely if: Patient had prior provoked seizure (neonatal, febrile); Sought medical attention for the first unprovoked seizure; Seizure was convulsive; Parent is college educated

Source: Berg AT, Loddenkemper T, Baca CB. Diagnostic delays in children with early onset epilepsy: Impact, reasons, and opportunites to improve care. Epilepsia 2014;55(1):123-32

Reasons for Delay

- Reasons for diagnostic delay
  - Parents not recognizing events as seizures 67%
  - Pediatricians missing or deferring diagnosis 21%
  - Neurologist deferring diagnosis after normal EEG 8%
  - Scheduling delays 16%
- Diagnostic delay associated with
  - 7.4 point drop in Vineland Scales of Adaptive Behavior motor score
  - 8.4 point drop in processing speed on WISC
  - 14.5 point drop in full scale IQ on WISC

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Source: Berg AT, Loddenkemper T, Baca CB. Diagnostic delays in children with early onset epilepsy: Impact, reasons, and opportunites to improve care. Epilepsia 2014;55(1):123-32

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When to Refer

- Referral to Neurology should happen at the point in which the practitioner feels the patient is beyond their comfort level or scope of practice. These include, but are not limited to:
  - **New onset seizures in a young child (under 3 years of age)***
  - **Suspected infantile spasms***
  - Type of seizure is unclear
  - Seizures are refractory to medication
  - Complicated medication management
  - Unclear etiology
  - Multiple neurologic diagnoses

***Refer early**

When To Refer

- Other reasons to refer:
  - Complicated medication management
  - Questions about prognosis arise
  - Other neurologic issues arise or complicate the patient's clinical status
- When to admit to the hospital for urgent care
  - Seizures are uncontrolled or prolonged
  - Emergent continuous video EEG monitoring is needed
  - Rapidly anticonvulsant medication changes are needed

Survey Question 1: Answer

An 18 y/o female, school student, comes for a follow-up visit. She had an event consistent with generalized tonic-clonic seizure 1 week ago, witnessed by a classmate, who reported that the seizure started suddenly with stiffening of whole body, followed by jerking movements of both arms and legs. The patient does not report any warning symptoms prior to the seizure. She was treated in the ER and sent home on maintenance dose of levetiracetam (LEV). A routine (30 min) EEG and head CT, obtained in the ER, were normal. The patient states that the week prior to the seizure, she usually slept no more than 2 hours/night due to school assignments. There is no family h/o seizures. Neurologic exam is normal.

Which of the following is the next best step in the management?

(1) Wean off Keppra

(2) Obtain brain MRI

(3) Obtain prolonged EEG, brain MRI, switch to phenytoin, and educate about seizure precautions

(4) Obtain additional history, prolonged EEG, and educate about seizure precautions

Survey Question 2: Answer

A 4 y/o boy is brought to the office for evaluation of events concerning for seizures, noted since last 3-4 months. The events typically occur in school and have been witnessed by the teacher. The patient will often start to cry, his breathing may become deep and/or fast. This may continue on and off for a few minutes. Sometimes there is low amplitude shaking of both the arms. The patient appears to remain aware throughout but may not respond to the teacher's voice. There have been several concerns about his bullying in the school since last 4-5 months. There is h/o epilepsy in maternal GM. He is typically developing, and has a normal neurological exam.

Which of the following is the next best step?

(1) Make a presumptive dx of epilepsy and start on carbamazepine

(2) Obtain a routine EEG and brain MRI

(3) Request parents and/or teacher to videotape the events and obtain a routine EEG

(4) Reassure the parents that these are not seizures and no further action is needed

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FROM THE AMERICAN ACADEMY OF PEDIATRICS

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Clinical Practice Guideline—Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

SUBCOMMITTEE ON FEBRILE SEIZURES

KEY WORD
seizure

ABBREVIATIONS
AAP—American Academy of Pediatrics
Hib—*Haemophilus influenzae* type b
EEG—electroencephalogram
CT—computed tomography

The recommendations in this report do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3318

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All clinical practice guidelines from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

abstract

FREE

OBJECTIVE: To formulate evidence-based recommendations for health care professionals about the diagnosis and evaluation of a simple febrile seizure in infants and young children 6 through 60 months of age and to revise the practice guideline published by the American Academy of Pediatrics (AAP) in 1996.

METHODS: This review included search and analysis of the medical literature published since the last version of the guideline. Physicians with expertise and experience in the fields of neurology and epilepsy, pediatrics, epidemiology, and research methodologies constituted a subcommittee of the AAP Steering Committee on Quality Improvement and Management. The steering committee and other groups within the AAP and organizations outside the AAP reviewed the guideline. The subcommittee member who reviewed the literature for the 1996 AAP practice guidelines searched for articles published since the last guideline through 2009, supplemented by articles submitted by other committee members. Results from the literature search were provided to the subcommittee members for review. Interventions of direct interest included lumbar puncture, electroencephalography, blood studies, and neuroimaging. Multiple issues were raised and discussed iteratively until consensus was reached about recommendations. The strength of evidence supporting each recommendation and the strength of the recommendation were assessed by the committee member most experienced in informatics and epidemiology and graded according to AAP policy.

CONCLUSIONS: Clinicians evaluating infants or young children after a simple febrile seizure should direct their attention toward identifying the cause of the child's fever. Meningitis should be considered in the differential diagnosis for any febrile child, and lumbar puncture should be performed if there are clinical signs or symptoms of concern. For any infant between 6 and 12 months of age who presents with a seizure and fever, a lumbar puncture is an option when the child is considered deficient in *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae* immunizations (ie, has not received scheduled immunizations as recommended), or when immunization status cannot be determined, because of an increased risk of bacterial meningitis. A lumbar puncture is an option for children who are pretreated with antibiotics. In general, a simple febrile seizure does not usually require further evaluation, specifically electroencephalography, blood studies, or neuroimaging. *Pediatrics* 2011;127:389–394

DEFINITION OF THE PROBLEM

This practice guideline provides recommendations for the neurodiagnostic evaluation of neurologically healthy infants and children 6 through 60 months of age who have had a simple febrile seizure and present for evaluation within 12 hours of the event. It replaces the 1996 practice parameter.[1] This practice guideline is not intended for patients who have had complex febrile seizures (prolonged, focal, and/or recurrent), and it does not pertain to children with previous neurologic insults, known central nervous system abnormalities, or history of afebrile seizures.

TARGET AUDIENCE AND PRACTICE SETTING

This practice guideline is intended for use by pediatricians, family physicians, child neurologists, neurologists, emergency physicians, nurse practitioners, and other health care providers who evaluate children for febrile seizures.

BACKGROUND

A febrile seizure is a seizure accompanied by fever (temperature ≥ 100.4°F or 38°C[2] by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age. Febrile seizures occur in 2% to 5% of all children and, as such, make up the most common convulsive event in children younger than 60 months. In 1976, Nelson and Ellenberg,[3] using data from the National Collaborative Perinatal Project, further defined febrile seizures as being either simple or complex. Simple febrile seizures were defined as primary generalized seizures that lasted for less than 15 minutes and did not recur within 24 hours. Complex febrile seizures were defined as focal, prolonged (≥15 minutes), and/or recurrent within 24 hours. Children who had simple febrile seizures had no evidence of increased mortality, hemiplegia, or mental retardation. During follow-up evaluation, the risk of epilepsy after a simple febrile seizure was shown to be only slightly higher than that of the general population, whereas the chief risk associated with simple febrile seizures was recurrence in one-third of the children. The authors concluded that simple febrile seizures are benign events with excellent prognoses, a conclusion reaffirmed in the 1980 consensus statement from the National Institutes of Health.[3,4]

The expected outcomes of this practice guideline include the following:

1. Optimize clinician understanding of the scientific basis for the neurodiagnostic evaluation of children with simple febrile seizures.
2. Aid the clinician in decision-making by using a structured framework.
3. Optimize evaluation of the child who has had a simple febrile seizure by detecting underlying diseases, minimizing morbidity, and reassuring anxious parents and children.
4. Reduce the costs of physician and emergency department visits, hospitalizations, and unnecessary testing.
5. Educate the clinician to understand that a simple febrile seizure usually does not require further evaluation, specifically electroencephalography, blood studies, or neuroimaging.

METHODOLOGY

To update the clinical practice guideline on the neurodiagnostic evaluation of children with simple febrile seizures,[1] the American Academy of Pediatrics (AAP) reconvened the Subcommittee on Febrile Seizures. The committee was chaired by a child neurologist and consisted of a neuroepidemiologist, 3 additional child neurologists, and a practicing pediatrician. All panel members reviewed and signed the AAP voluntary disclosure and conflict-of-interest form. No conflicts were reported. Participation in the guideline process was voluntary and not paid. The guideline was reviewed by members of the AAP Steering Committee on Quality Improvement and Management; members of the AAP Section on Administration and Practice Management, Section on Developmental and Behavioral Pediatrics, Section on Epidemiology, Section on Infectious Diseases, Section on Neurology, Section on Neurologic Surgery, Section on Pediatric Emergency Medicine, Committee on Pediatric Emergency Medicine, Committee on Practice and Ambulatory Medicine, Committee on Child Health Financing, Committee on Infectious Diseases, Committee on Medical Liability and Risk Management, Council on Children With Disabilities, and Council on Community Pediatrics; and members of outside organizations including the Child Neurology Society, the American Academy of Neurology, the American College of Emergency Physicians, and members of the Pediatric Committee of the Emergency Nurses Association.

A comprehensive review of the evidence-based literature published from 1996 to February 2009 was conducted to discover articles that addressed the diagnosis and evaluation of children with simple febrile seizures. Preference was given to population-based studies, but given the scarcity of such studies, data from hospital-based studies, groups of young children with febrile illness, and comparable groups were reviewed. Decisions were made on the basis of a systematic grading of the quality of evidence and strength of recommendations.

In the original practice parameter,[1] 203 medical journal articles were reviewed and abstracted. An additional 372 articles were reviewed and abstracted for this update. Emphasis was placed on articles that differentiated simple febrile seizures from other types of seizures. Tables were constructed from the 70 articles that best fit these criteria.

The evidence-based approach to guideline development requires that the evidence in support of a recommendation be identified, appraised, and summarized and that an explicit link between

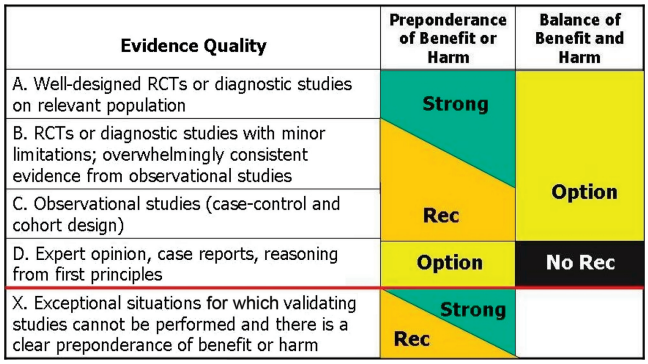

FIGURE 1

Integrating evidence quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is carried out leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation. RCT indicates randomized controlled trial; Rec, recommendation.

evidence and recommendations be defined. Evidence-based recommendations reflect the quality of evidence and the balance of benefit and harm that is anticipated when the recommendation is followed. The AAP policy statement "Classifying Recommendations for Clinical Practice Guidelines"[5] was followed in designating levels of recommendations (see Fig 1).

KEY ACTION STATEMENTS

Action Statement 1

Action Statement 1a

A lumbar puncture should be performed in any child who presents with a seizure and a fever and has meningeal signs and symptoms (eg, neck stiffness, Kernig and/or Brudzinski signs) or in any child whose history or examination suggests the presence of meningitis or intracranial infection.

- Aggregate evidence level: B (overwhelming evidence from observational studies).
- Benefits: Meningeal signs and symptoms strongly suggest meningitis, which, if bacterial in etiology, will likely be fatal if left untreated.
- Harms/risks/costs: Lumbar puncture is an invasive and often painful procedure and can be costly.
- Benefits/harms assessment: Preponderance of benefit over harm.
- Value judgments: Observational data and clinical principles were used in making this judgment.
- Role of patient preferences: Although parents may not wish to have their child undergo a lumbar puncture, health care providers should explain that if meningitis is not diagnosed and treated, it could be fatal.
- Exclusions: None.
- Intentional vagueness: None.
- Policy level: Strong recommendation.

Action Statement 1b

In any infant between 6 and 12 months of age who presents with a seizure and fever, a lumbar puncture is an option when the child is considered deficient in *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae* immunizations (ie, has not received scheduled immunizations as recommended) or when immunization status cannot be determined because of an increased risk of bacterial meningitis.

- Aggregate evidence level: D (expert opinion, case reports).
- Benefits: Meningeal signs and symptoms strongly suggest meningitis, which, if bacterial in etiology, will likely be fatal or cause significant long-term disability if left untreated.
- Harms/risks/costs: Lumbar puncture is an invasive and often painful procedure and can be costly.
- Benefits/harms assessment: Preponderance of benefit over harm.
- Value judgments: Data on the incidence of bacterial meningitis from before and after the existence of immunizations against Hib and *S pneumoniae* were used in making this recommendation.
- Role of patient preferences: Although parents may not wish their child to undergo a lumbar puncture, health care providers should explain that in the absence of complete immunizations, their child may be at risk of having fatal bacterial meningitis.
- Exclusions: This recommendation applies only to children 6 to 12 months of age. The subcommittee felt that clinicians would recognize symptoms of meningitis in children older than 12 months.
- Intentional vagueness: None.
- Policy level: Option.

Action Statement 1c

A lumbar puncture is an option in the child who presents with a seizure and fever and is pretreated with antibiotics, because antibiotic treatment can mask the signs and symptoms of meningitis.

- Aggregate evidence level: D (reasoning from clinical experience, case series).
- Benefits: Antibiotics may mask meningeal signs and symptoms but may be insufficient to eradicate meningitis; a diagnosis of meningitis, if bacterial in etiology, will likely be fatal if left untreated.
- Harms/risks/costs: Lumbar puncture is an invasive and often painful procedure and can be costly.

- Benefits/harms assessment: Preponderance of benefit over harm.
- Value judgments: Clinical experience and case series were used in making this judgment while recognizing that extensive data from studies are lacking.
- Role of patient preferences: Although parents may not wish to have their child undergo a lumbar puncture, medical providers should explain that in the presence of pretreatment with antibiotics, the signs and symptoms of meningitis may be masked. Meningitis, if untreated, can be fatal.
- Exclusions: None.
- Intentional vagueness: Data are insufficient to define the specific treatment duration necessary to mask signs and symptoms. The committee determined that the decision to perform a lumbar puncture will depend on the type and duration of antibiotics administered before the seizure and should be left to the individual clinician.
- Policy level: Option.

The committee recognizes the diversity of past and present opinions regarding the need for lumbar punctures in children younger than 12 months with a simple febrile seizure. Since the publication of the previous practice parameter,[1] however, there has been widespread immunization in the United States for 2 of the most common causes of bacterial meningitis in this age range: Hib and *S pneumoniae*. Although compliance with all scheduled immunizations as recommended does not completely eliminate the possibility of bacterial meningitis from the differential diagnosis, current data no longer support routine lumbar puncture in well-appearing, fully immunized children who present with a simple febrile seizure.[6–8] Moreover, although approximately 25% of young children with meningitis have seizures as the presenting sign of the disease, some are either obtunded or comatose when evaluated by a physician for the seizure, and the remainder most often have obvious clinical signs of meningitis (focal seizures, recurrent seizures, petechial rash, or nuchal rigidity).[9–11] Once a decision has been made to perform a lumbar puncture, then blood culture and serum glucose testing should be performed concurrently to increase the sensitivity for detecting bacteria and to determine if there is hypoglycorrhachia characteristic of bacterial meningitis, respectively.

Recent studies that evaluated the outcome of children with simple febrile seizures have included populations with a high prevalence of immunization.[7,8] Data for unimmunized or partially immunized children are lacking. Therefore, lumbar puncture is an option for young children who are considered deficient in immunizations or those in whom immunization status cannot be determined. There are also no definitive data on the outcome of children who present with a simple febrile seizure while already on antibiotics. The authors were unable to find a definition of "pretreated" in the literature, so they consulted with the AAP Committee on Infectious Diseases. Although there is no formal definition, pretreatment can be considered to include systemic antibiotic therapy by any route given within the days before the seizure. Whether pretreatment will affect the presentation and course of bacterial meningitis cannot be predicted but will depend, in part, on the antibiotic administered, the dose, the route of administration, the drug's cerebrospinal fluid penetration, and the organism causing the meningitis. Lumbar puncture is an option in any child pretreated with antibiotics before a simple febrile seizure.

Action Statement 2

An electroencephalogram (EEG) should not be performed in the evaluation of a neurologically healthy child with a simple febrile seizure.

- Aggregate evidence level: B (overwhelming evidence from observational studies).
- Benefits: One study showed a possible association with paroxysmal EEGs and a higher rate of afebrile seizures.[12]
- Harms/risks/costs: EEGs are costly and may increase parental anxiety.
- Benefits/harms assessment: Preponderance of harm over benefit.
- Value judgments: Observational data were used for this judgment.
- Role of patient preferences: Although an EEG might have limited prognostic utility in this situation, parents should be educated that the study will not alter outcome.
- Exclusions: None.
- Intentional vagueness: None.
- Policy level: Strong recommendation.

There is no evidence that EEG readings performed either at the time of presentation after a simple febrile seizure or within the following month are predictive of either recurrence of febrile seizures or the development of afebrile seizures/epilepsy within the next 2 years.[13,14] There is a single study that found that a paroxysmal EEG was associated with a higher rate of afebrile seizures.[12] There is no evidence that interventions based on this test would alter outcome.

Action Statement 3

The following tests should not be performed routinely for the sole purpose of identifying the cause of a simple febrile seizure: measurement of serum electrolytes, calcium, phosphorus, magnesium, or blood glucose or complete blood cell count.

- Aggregate evidence level: B (overwhelming evidence from observational studies).
- Benefits: A complete blood cell count may identify children at risk for bacte-

remia; however, the incidence of bacteremia in febrile children younger than 24 months is the same with or without febrile seizures.

- Harms/risks/costs: Laboratory tests may be invasive and costly and provide no real benefit.
- Benefits/harms assessment: Preponderance of harm over benefit.
- Value judgments: Observational data were used for this judgment.
- Role of patient preferences: Although parents may want blood tests performed to explain the seizure, they should be reassured that blood tests should be directed toward identifying the source of their child's fever.
- Exclusions: None.
- Intentional vagueness: None.
- Policy level: Strong recommendation.

There is no evidence to suggest that routine blood studies are of benefit in the evaluation of the child with a simple febrile seizure.[15–18] Although some children with febrile seizures have abnormal serum electrolyte values, their condition should be identifiable by obtaining appropriate histories and performing careful physical examinations. It should be noted that as a group, children with febrile seizures have relatively low serum sodium concentrations. As such, physicians and caregivers should avoid overhydration with hypotonic fluids.[18] Complete blood cell counts may be useful as a means of identifying young children at risk of bacteremia. It should be noted, however, that the incidence of bacteremia in children younger than 24 months with or without febrile seizures is the same. When fever is present, the decision regarding the need for laboratory testing should be directed toward identifying the source of the fever rather than as part of the routine evaluation of the seizure itself.

Action Statement 4

Neuroimaging should not be performed in the routine evaluation of the child with a simple febrile seizure.

- Aggregate evidence level: B (overwhelming evidence from observational studies).
- Benefits: Neuroimaging might provide earlier detection of fixed structural lesions, such as dysplasia, or very rarely, abscess or tumor.
- Harms/risks/costs: Neuroimaging tests are costly, computed tomography (CT) exposes children to radiation, and MRI may require sedation.
- Benefits/harms assessment: Preponderance of harm over benefit.
- Value judgments: Observational data were used for this judgment.
- Role of patient preferences: Although parents may want neuroimaging performed to explain the seizure, they should be reassured that the tests carry risks and will not alter outcome for their child.
- Exclusions: None.
- Intentional vagueness: None.
- Policy level: Strong recommendation.

The literature does not support the use of skull films in evaluation of the child with a febrile seizure.[15,19] No data have been published that either support or negate the need for CT or MRI in the evaluation of children with simple febrile seizures. Data, however, show that CT scanning is associated with radiation exposure that may escalate future cancer risk. MRI is associated with risks from required sedation and high cost.[20,21] Extrapolation of data from the literature on the use of CT in neurologically healthy children who have generalized epilepsy has shown that clinically important intracranial structural abnormalities in this patient population are uncommon.[22,23]

CONCLUSIONS

Clinicians evaluating infants or young children after a simple febrile seizure should direct their attention toward identifying the cause of the child's fever. Meningitis should be considered in the differential diagnosis for any febrile child, and lumbar puncture should be performed if the child is ill-appearing or if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6 to 12 months of age who is deficient in Hib and *S pneumoniae* immunizations or for whom immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. In general, a simple febrile seizure does not usually require further evaluation, specifically EEGs, blood studies, or neuroimaging.

SUBCOMMITTEE ON FEBRILE SEIZURES, 2002–2010

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OVERSIGHT BY THE STEERING COMMITTEE ON QUALITY IMPROVEMENT AND MANAGEMENT, 2009–2011

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Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure

Subcommittee on Febrile Seizures

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Febrile Seizures: Risks, Evaluation, and Prognosis

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Febrile seizures are common in the first five years of life, and many factors that increase seizure risk have been identified. Initial evaluation should determine whether features of a complex seizure are present and identify the source of fever. Routine blood tests, neuroimaging, and electroencephalography are not recommended, and lumbar puncture is no longer recommended in patients with uncomplicated febrile seizures. In the unusual case of febrile status epilepticus, intravenous lorazepam and buccal midazolam are first-line agents. After an initial febrile seizure, physicians should reassure parents about the low risk of long-term effects, including neurologic sequelae, epilepsy, and death. However, there is a 15 to 70 percent risk of recurrence in the first two years after an initial febrile seizure. This risk is increased in patients younger than 18 months and those with a lower fever, short duration of fever before seizure onset, or a family history of febrile seizures. Continuous or intermittent antiepileptic or antipyretic medication is not recommended for the prevention of recurrent febrile seizures. (*Am Fam Physician.* 2012;85(2):149-153. Copyright © 2012 American Academy of Family Physicians.)

▶ **Patient information:** A handout on febrile seizures is available at http://familydoctor.org/066.xml.

Febrile seizures are the most common seizures of childhood, occurring in 2 to 5 percent of children six months to five years of age.[1] As defined by the American Academy of Pediatrics (AAP), febrile seizures occur in the absence of intracranial infection, metabolic disturbance, or history of afebrile seizures, and are classified as simple or complex[1,2] *(Table 1[1,3])*. Simple febrile seizures represent 65 to 90 percent of febrile seizures[2] and require all of the following features: a duration of less than 15 minutes, generalized in nature, a single occurrence in a 24-hour period, and no previous neurologic problems.[1]

Risk Factors

Risk factors for febrile seizures include developmental delay, discharge from a neonatal unit after 28 days, day care attendance, viral infections, a family history of febrile seizures, certain vaccinations, and possibly iron and zinc deficiencies.[4-13] Febrile seizures may occur before or soon after the onset of fever, with the likelihood of seizure increasing with the child's temperature and not with the rate of temperature rise.[4]

Vaccinations associated with increased risk include 2010 Southern Hemisphere seasonal influenza trivalent inactivated vaccine (Fluvax Junior and Fluvax); diphtheria and tetanus toxoids and whole-cell pertussis (DTP); and measles, mumps, and rubella (MMR).[13-15] A Cochrane review and a review of 530,000 children receiving the MMR vaccine showed that the risk of febrile seizures increased only during the first two weeks after vaccination, was small (an additional one or two febrile seizures per 1,000 vaccinations), and was likely related to fever from the vaccine.[6,9]

A genetic predisposition for febrile seizures has been postulated, although no susceptibility gene has been identified. Genetic

Table 1. Classification of Febrile Seizures

Simple (all of the following)
Duration of less than 15 minutes
Generalized
No previous neurologic problems
Occur once in 24 hours
Complex (any of the following)
Duration of more than 15 minutes
Focal
Recurs within 24 hours

Adapted with permission from Millar JS. Evaluation and treatment of the child with febrile seizure. Am Fam Physician. *2006;73(10):1761, with additional information from reference 1.*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References	Comments
Routine laboratory tests, electroencephalography, and neuroimaging are not recommended in patients with simple febrile seizures.	C	17, 19-21, 24, 25	Consensus guideline and retrospective cohort studies
Parents should be reassured after a simple febrile seizure that there is no negative impact on intellect or behavior, and no increased risk of death.	B	1, 28, 29	Consensus guideline and prospective cohort studies
Use of long-term continuous or intermittent antiepileptic medication after a first simple febrile seizure is not recommended because of potential adverse effects.	B	1, 32, 33	Consensus guideline and randomized controlled trials
Use of antipyretic agents at the onset of fever is not effective at reducing simple febrile seizure recurrence.	A	1, 31	Consensus guideline and randomized controlled trial

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

abnormalities have been reported in persons with febrile epilepsy syndromes, such as severe myoclonic epilepsy in infancy and generalized epilepsy with febrile seizures plus (GEFS+).[14] Most causes of febrile seizures are multifactorial, with two or more genetic and contributing environmental factors.

Case-control studies suggest that iron and zinc deficiencies may also be risk factors for febrile seizures. One study of febrile seizures in Indian children three months to five years of age showed lower serum zinc levels in patients with seizures compared with age-matched febrile patients without seizures.[7] In another study, children with febrile seizures had nearly two times the incidence of iron deficiency compared with febrile children who did not have seizures.[8]

Viral infections are a common cause of fever that triggers febrile seizures. A particular risk for febrile seizure is associated with primary human herpesvirus 6 infection, which is typically acquired during the first two years of life. In a case-control study, polymerase chain reaction testing and antibody titers suggested that 10 of 55 children (18 percent) who experienced a first febrile seizure had acute herpesvirus 6 infection, whereas none of the 85 children with fever but no seizure had evidence of such infection.[12] Other common viral infections, such as influenza, adenovirus, and parainfluenza, are associated with simple and complex febrile seizures.[11]

Evaluation

Children should be promptly evaluated after an initial seizure. Most patients with febrile seizures present for medical care after resolution of the seizure and return to full alertness within an hour of the seizure.[16] The initial evaluation should focus on determining the source of the fever.[3,17] Parents should be questioned about a family history of febrile seizures or epilepsy, immunizations, recent antibiotic use, duration of the seizure, a prolonged postictal phase, and any focal symptoms. During the examination, attention should be given to the presence of meningeal signs and to the child's level of consciousness. In a 20-year retrospective review of 526 cases of bacterial meningitis, 93 percent of patients presented with altered consciousness.[18]

Routine laboratory studies in patients with simple febrile seizures are discouraged because electrolyte abnormalities and serious bacterial illnesses are rare.[16,19,20] In a retrospective review of 379 children with simple febrile seizures, only eight were found to have bacteremia.[21] *Streptococcus pneumoniae* was isolated in seven of the eight children, in an era before routine pneumococcal vaccination.

The AAP recently updated its 1996 guideline regarding the use of lumbar puncture in children with simple febrile seizures.[17] A lumbar puncture is now an option when evaluating children six to 12 months of age whose immunization status for *Haemophilus influenzae* type b and *S. pneumoniae* is incomplete or unknown, and in those pretreated with antibiotics.[17] This differs from the previous recommendation that lumbar puncture be performed in all children younger than 12 months and strongly considered in

those 12 to 18 months of age. Currently, as in the previous guideline, a lumbar puncture is strongly recommended in those with meningeal signs and in those with any other findings from the history or physical examination that are concerning for intracranial infection.[17,19]

The AAP's updated recommendations are supported by evidence from observational studies, as well as two reviews.[16] In the 20-year retrospective review mentioned previously, no patients with bacterial meningitis presented with only fever and seizure.[18] In a more recent review of 704 patients with simple febrile seizures and no other findings concerning for bacterial meningitis, no cases of meningitis were identified.[22] A second study reviewed 526 cases of complex febrile seizures and found only three cases of bacterial meningitis.[23] Of these, one patient was unresponsive at presentation, and another had clear indications for lumbar puncture based on physical findings. The third was treated for bacterial meningitis after she had a negative lumbar puncture in the presence of *S. pneumoniae* bacteremia.

Electroencephalography has not been shown to predict recurrence of febrile seizures or future epilepsy in patients with simple febrile seizures.[17,19] Routine neuroimaging after simple febrile seizures is discouraged; it also has no additional diagnostic or prognostic value, and in the case of computed tomography, carries a small increased risk of cancer.[16,19,24] Even after first complex febrile seizures, neuroimaging is not likely to be helpful in well-appearing children. In a review of 71 patients with first complex seizures, none had intracranial findings necessitating acute medical or surgical intervention.[25] Electroencephalography and neuroimaging may be considered in children with neurologic abnormalities on examination and in those with recurrent febrile seizures.[26]

Acute Treatment

Although most febrile seizures have resolved by the time of presentation, physicians should be prepared to treat patients with febrile status epilepticus. In the acute setting, intravenous lorazepam (Ativan) in a dose of 0.1 mg per kg is the treatment of choice for acute tonic-clonic pediatric seizures. A Cochrane review found lorazepam to be as effective as diazepam (Valium), with fewer adverse effects and less need for additional antiepileptic agents.[27] The same study found buccal midazolam to be superior to rectal diazepam (Diastat) when intravenous administration is not possible.

Table 2. Risk of Recurrence After an Initial Febrile Seizure

Risk factors	*Number of risk factors*	*2-year risk of recurrence (%)*
Age < 18 months	0	14
Duration of fever < 1 hour before seizure onset	1	> 20
First-degree relative with febrile seizure	2	> 30
Temperature < 104°F (40°C)	3	> 60
	4	> 70

Information from reference 30.

Prognosis and Long-term Management

Physicians can play a vital role in reassuring families about the good prognosis after a febrile seizure. Key concerns to be addressed include the risks of neurologic morbidity (including epilepsy), mortality, and seizure recurrence.

Parents should be reassured that children without underlying developmental problems do not seem to have lasting neurologic effects from febrile seizures. A population-based study in the United Kingdom that included 381 children with febrile seizures reported that those with febrile seizures perform as well as others academically, intellectually, and behaviorally when assessed at 10 years of age.[28] Parents should be told that mortality from febrile seizures is very rare—so rare that it is difficult to assess accurately. A large cohort study in Denmark examined mortality rates in 1.6 million children.[29] There was a slight increase in mortality (adjusted mortality rate ratio of 1.99) during the two years after a complex febrile seizure, but no significant increase among those with simple febrile seizures.

Parents should be warned that febrile seizures reoccur frequently. One cohort study found that 32 percent of children presenting with an initial febrile seizure later had additional febrile seizures, 75 percent of which occurred within one year.[30] Risk factors and risk of recurrence after an initial

Table 3. Risk Factors for Future Epilepsy After a Febrile Seizure

Complex febrile seizure*
Family history of epilepsy
Fever duration < 1 hour before seizure onset
Neurodevelopmental abnormality (e.g., cerebral palsy, hydrocephalus)

**—Febrile seizures with multiple complex features are a possible risk factor.*

Adapted with permission from Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. *2002;17(suppl 1):S46.*

febrile seizure are provided in *Table 2*.[30] The risk of recurrence is similar between simple and complex febrile seizures.

Multiple agents have been evaluated in the prevention of recurrent simple febrile seizures. Continuous use of phenobarbital, primidone (Mysoline), and valproic acid (Depakene) has proved effective in reducing recurrence of simple febrile seizures.[1] However, these agents are not recommended because of associated adverse effects, the burden of long-term compliance, and a lack of data showing a reduced risk of future epilepsy with prevention of recurrent simple febrile seizures.[1]

Intermittent use of antipyretics or anticonvulsants at the onset of fever is not recommended. No studies have shown a reduction in recurrent simple febrile seizures when antipyretics are given at the onset of fever. In a randomized, placebo-controlled, double-blind trial, no decrease in febrile seizure recurrence was observed with scheduled administration of maximal doses of acetaminophen or ibuprofen.[31] Although intermittent use of oral diazepam at the onset of fever is effective at reducing recurrence of simple febrile seizures, the AAP does not recommend it because of potential adverse effects and because many recurrent febrile seizures occur before recognition of fever.[1,32,33] If parental anxiety is high, oral diazepam given at the onset of a child's fever may be considered. Additionally, rectal administration of diazepam for abortive use at home may be considered in those with an initial prolonged febrile seizure and in those at highest risk of recurrence.

Some population cohort studies have indicated that children with a history of febrile seizures have an increased but still low rate of epilepsy.[34] A Danish cohort study of 1.54 million persons found that the long-term risk of epilepsy is increased 5.43-fold after febrile seizures, but did not distinguish between simple and complex febrile seizures.[34] Risk factors included a family history of epilepsy, cerebral palsy, and Apgar score less than 7 at five minutes. Parents can be reassured that the risk of epilepsy after an initial simple febrile seizure is approximately 2 percent.[35,36] This risk increases in children with complex febrile seizures. In one study, children with one complex seizure feature had a risk of 6 to 8 percent.[36] In those with two or three complex features, the risk was 17 to 22 percent and 49 percent, respectively. Risk factors for the development of future epilepsy are included in *Table 3*.[37]

Data Sources: We used the term febrile seizures to search PubMed for all articles from 2004 to the present for children younger than 18 years. Another search was performed with no date limits using the term febrile convulsion. The same terms and limitations were used to search PubMed Clinical Inquiries in the diagnosis and therapy categories. The National Guideline Clearinghouse, Cochrane Database of Systematic Reviews, UpToDate, Dynamed, Agency for Healthcare Research and Quality, Institute for Clinical Systems Improvement, U.S. Preventive Services Task Force, Ovid Evidence-Based Medicine Reviews (including systematic reviews from Cochrane, DARE, and ACP Journal Club), and Bandolier were also searched using the term febrile seizure. Search date: October 2010.

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Author disclosure: No relevant financial affiliations to disclose.

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The Definition of Epilepsy

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Maslah Saul MD Professor of Neurology
Director, Stanford Epilepsy Center

In 2005, the ILAE released a conceptual definition of seizures and epilepsy, followed by an operational (practical) definition in 2014. The key changes were: epilepsy can exist after two unprovoked seizures more than 24 hours apart (the old definition) or one unprovoked seizure when the risk for another is known to be high (>60%); reflex seizures and seizures that are part of an epilepsy syndrome constitute epilepsy; epilepsy may be considered resolved when an age-dependent syndrome is outgrown or when a person is seizure-free for at least 10 years, the last 5 off anti-seizure medicines.

ILAE OFFICIAL REPORT

Epilepsia
The Journal of the International League Against Epilepsy

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014

Epilepsy is a disease of the brain defined by any of the following conditions

1. A least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Seizure versus Epilepsy

- **A seizure is the event**
- **Epilepsy is the disease associated with spontaneously recurring seizures**

Conceptual Definition of Epilepsy

Epilepsia, **46**(4):470-472, 2005
Blackwell Publishing, Inc.

Epileptic Seizures and Epilepsy: Definitions Proposed By the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).

Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr.

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

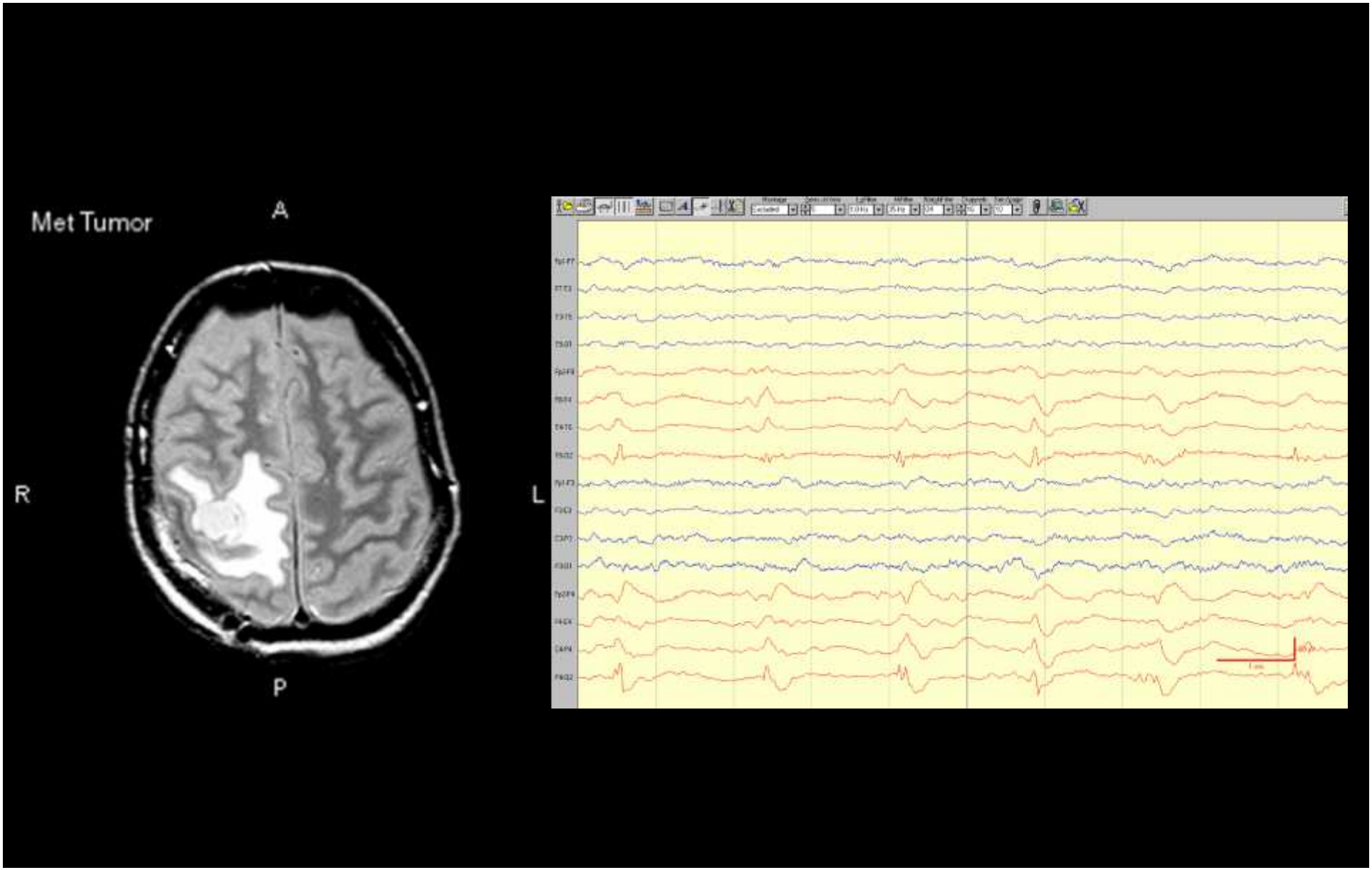
Traditional Epilepsy Definition

Epilepsy is a disorder characterized by two or more unprovoked seizures occurring more than 24 hours apart.

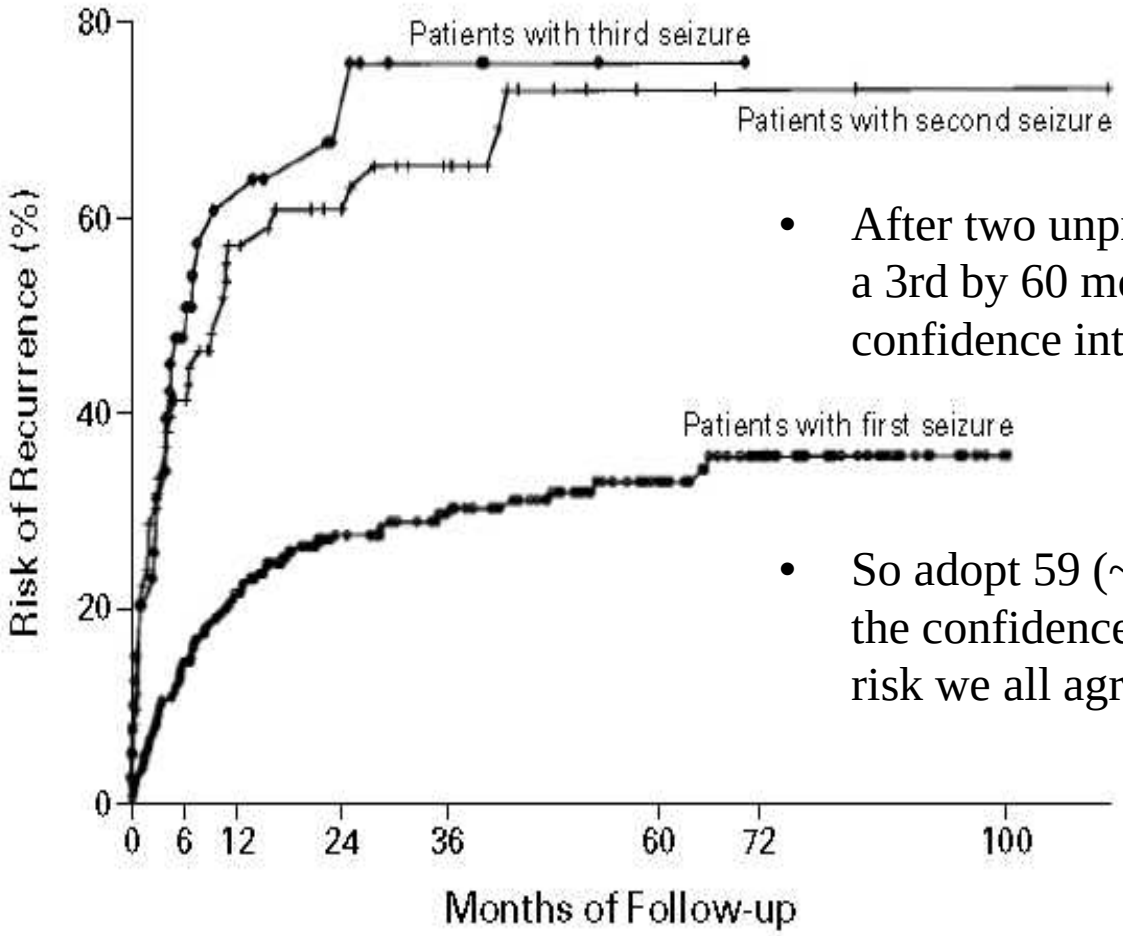
Concise, easy to apply, known to many, but . . .

- **Some people now are treated as if they have epilepsy after 1 seizure**
- **A person can never outgrow epilepsy**
- **Can have an epilepsy syndrome (e.g., BRE), but not epilepsy**
- **Those with photic or reflex seizures are not defined as having epilepsy**

- **Some people now are treated as if they have epilepsy after 1 seizure**



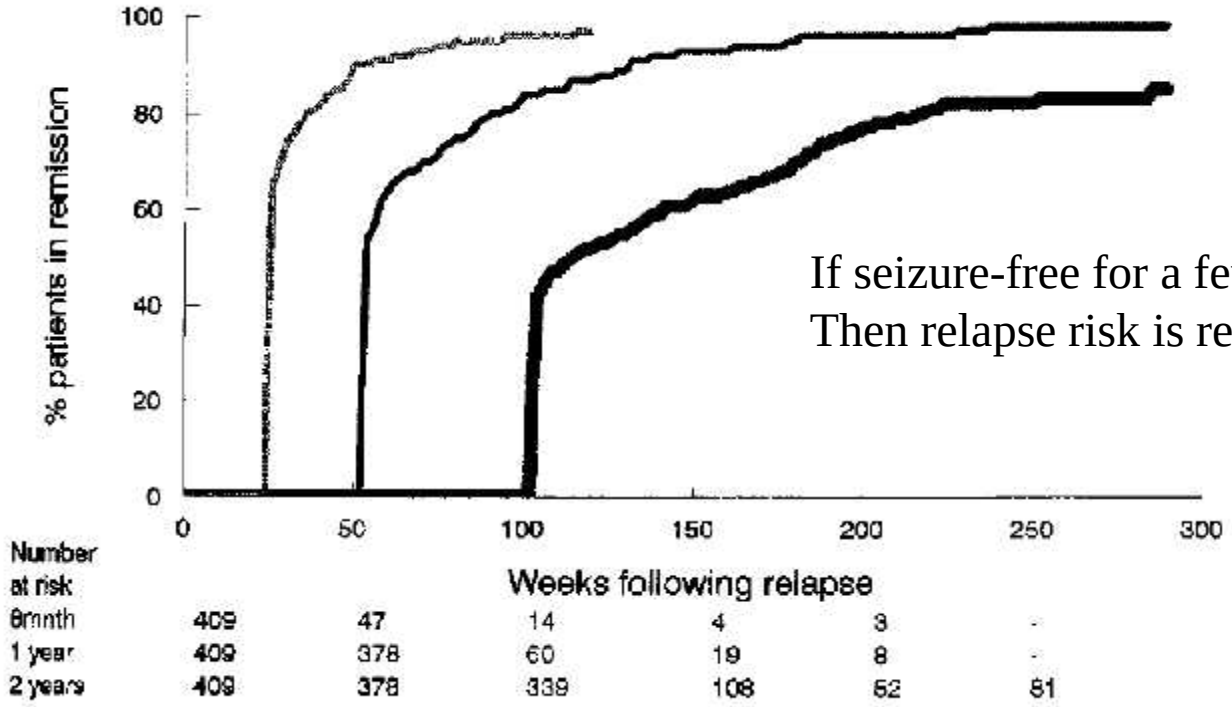
- **Risk of epilepsy after 2 seizures**



- After two unprovoked seizures, the risk of a 3rd by 60 months is 73% (59-87%, 95% confidence intervals.
- So adopt 59 (~ 60%) as the lower end of the confidence interval for the recurrence risk we all agree is epilepsy.

Hauser et al. Risk of recurrent seizures after two unprovoked seizures. NEJM 1998;338:429.

- **Can a person outgrow epilepsy ?**



If seizure-free for a few years,
Then relapse risk is relatively low.

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 Group. Epilepsia. 1996;37:1043-50.

Epilepsy Resolved

- Epilepsy is now considered to be resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

* Avoiding preconceptions associated with the words “cure” and “remission.”

“Resolved” has the connotation of “no longer present,” but it does not guarantee that epilepsy will never come back

Fisher et al, Epilepsia 55 (4): 475-482, 2014

Reflex Epilepsies

- Despite the fact that seizures are “provoked” in reflex epilepsies, these are considered epilepsy, because…
- If the seizure threshold were not altered, these precipitants would typically not cause seizures
  - e.g., photosensitive epilepsy, eating epilepsy

- “The revised definition places no burden on the treating physician to specify recurrence risk in a particular circumstance.
- In the absence of clear information about recurrence risk, or even knowledge of such information, the default definition of epilepsy originates at the second unprovoked seizure.
- On the other hand, if information is available to indicate that risk for a second seizure exceeds that which is usually considered to be epilepsy (about 60%), then epilepsy can be considered to be present”

Fisher et al, Epilepsia 55 (4): 475-482, 2014

Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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Courtesy of Jacqueline French

AAN Guideline

Conclusion:

- Adults with an unprovoked first seizure should be informed that sz recurrence risk is greatest early within the first 2 years (21%–45%) (Level A), and **clinical variables associated with increased risk may include:**
  - a prior brain insult (Level A),
  - an epileptiform EEG (Level A),
  - an abnormal CT/MRI(Level B)
  - a nocturnal seizure (Level B).

Courtesy of Jacqueline French

AAN Guideline

- Immediate antiepileptic drug (AED) therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first 2 years (Level B)
- **Clinicians' recommendations whether to initiate immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the adverse events of AED therapy.**

Courtesy of Jacqueline French

These are not Epilepsy because there is small risk of a seizure in the absence of a precipitating factor

- Febrile seizures in children age 0.5 – 6 years old
- Alcohol-withdrawal seizures
- Metabolic seizures (sodium, calcium, magnesium, glucose, oxygen)
- Toxic seizures (drug reactions or withdrawal, renal failure)
- Convulsive syncope
- Acute concussive convulsion
- Seizures within first week after brain trauma, infection or stroke

ILAE Definition of Acute Symptomatic Epilepsy

Acute symptomatic seizures are events, occurring in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious, or due to inflammation. The interval between the insult and seizure may vary due to the underlying clinical condition.

- Acute symptomatic seizures have also been called:
  - Reactive seizures
  - Provoked seizures
  - Situation-related seizures

Beghi et al. Epilepsia 2010;51:671-675 Courtesy of Dale Hesdorffer

Defining time in acute symptomatic seizures

Events within 1 week of:

- Stroke
- TBI
- Anoxic encephalopathy
- Intracranial surgery
- First identification of subdural hematoma
- Presence of an active CNS infection
- During an active phase of multiple sclerosis or other autoimmune disease

Beghi et al. Epilepsia 2010;51:671-675 Courtesy of Dale Hesdorffer

Acute symptomatic afebrile seizures: Incidence, proportion and recurrence

- **Age-adjusted incidence of acute symptomatic seizures was 39/100,000 in Rochester, MN**
- **The acute symptomatic seizure incidence was 29/100,000 in Gironde France**
- **These both represented 40% of all afebrile seizures in the community**

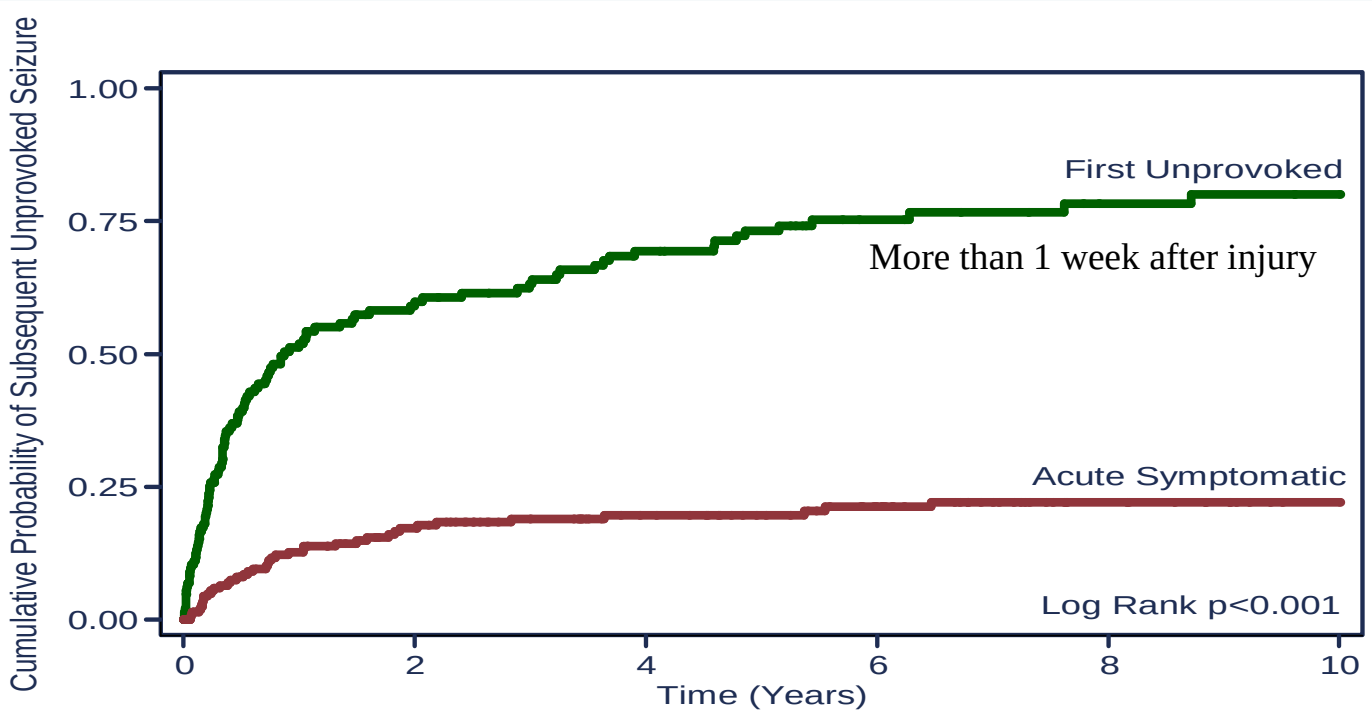
<u>Recurrent seizures</u>

- **Acute symptomatic seizures are unlikely to be recurrent**
- **Unprovoked seizures are often recurrent**

Annegers et al. Epilepsia 1995;36:327-333; Loiseau et al. These, 1987.

Courtesy of Dale Hesdorffer

Cumulative risk for recurrent unprovoked seizure, Rochester 1955-84: Structural Etiologies: CNS infection, stroke, TBI



Univariate RR=0.2, 95% CI=0.1-0.3
Adjusted RR=0.02 (95% CI=0.2-0.4), adjusting for age gender and SE

Hesdorffer et al. Epilepsia 2009

Courtesy of Dale Hesdorffer

HYPOTHETICAL CASE: Two seizures

A 25 year-old woman has two unprovoked seizures one year apart.

HYPOTHETICAL CASE: Two seizures

A 25 year-old woman has two unprovoked seizures one year apart.

Comment: This person has epilepsy, according to both the old and new definitions.

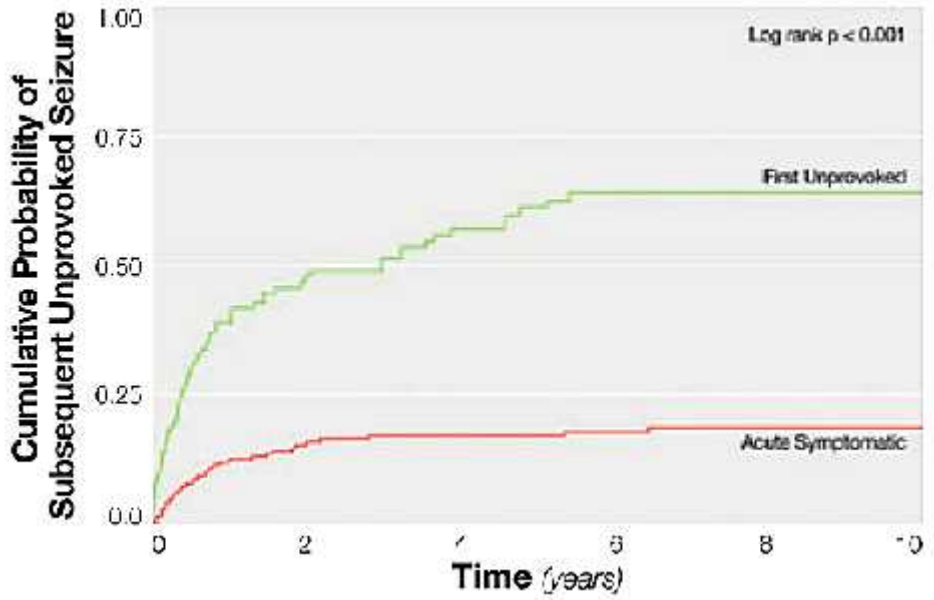
HYPOTHETICAL CASE: Stroke & Seizure

A 65 year-old man had a left middle cerebral artery stroke 6 weeks ago and now presented with an unprovoked seizure.

HYPOTHETICAL CASE: Stroke & Seizure

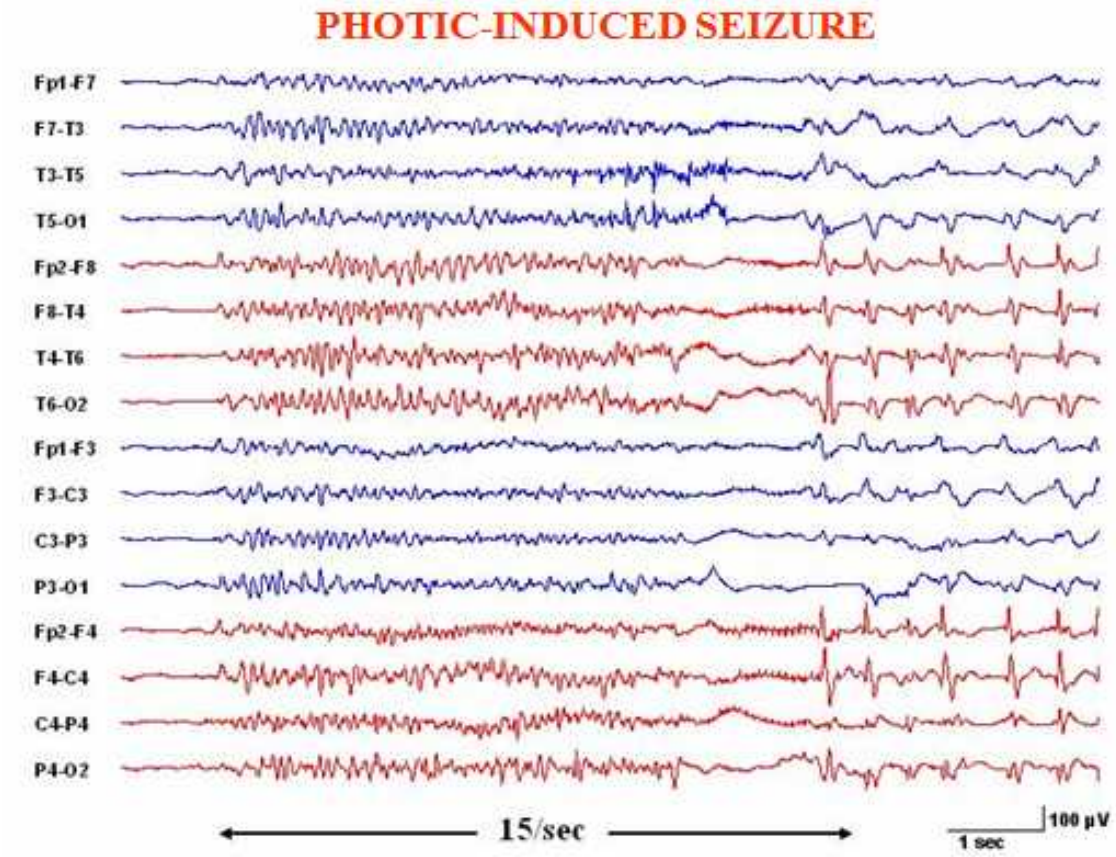
A 65 year-old man had a left middle cerebral artery stroke 6 weeks ago and now presented with an unprovoked seizure.

Comment: With a seizure in this time relation to a stroke (or brain infection or brain trauma) the literature (Hesdorffer et al., 2009) suggests a high (> 70%) risk of another unprovoked seizure. Therefore, in the new (but not the old) definition, this man would have epilepsy.



HYPOTHETICAL CASE: Photic Seizure

A 6 year-old boy has had 2 seizures 3 days apart while playing a videogame involving flashing lights. There have been no other seizures. EEG shows an abnormal photoparoxysmal response.



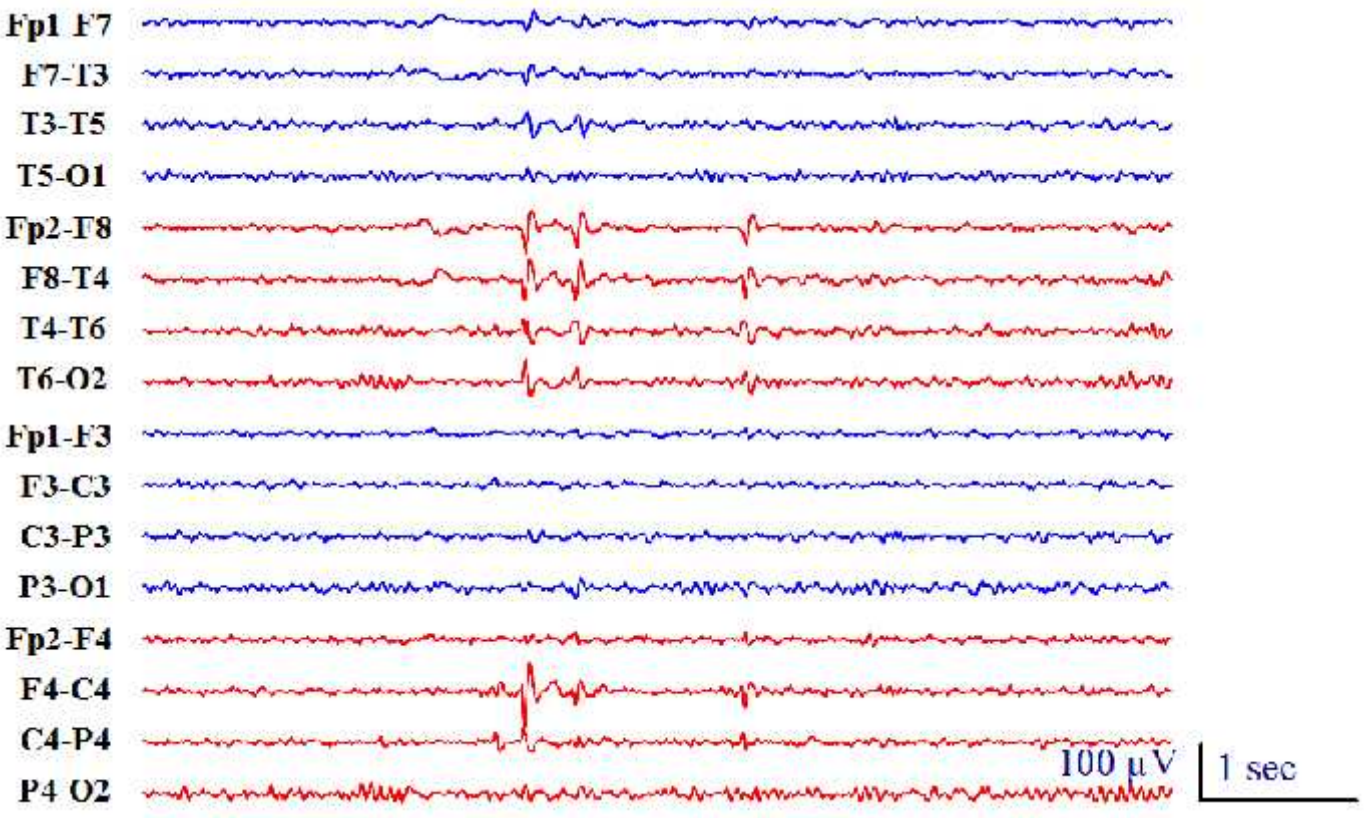
HYPOTHETICAL CASE: Photic Seizure

A 6 year-old boy has had 2 seizures 3 days apart while playing a videogame involving flashing lights. There have been no other seizures. EEG shows an abnormal photoparoxysmal response.

Comment: This boy has epilepsy according to the new definition (but not the old), even though the seizures are provoked by lights, since there is an abnormal enduring predisposition to have seizures with light flashes.

Benign Epilepsy with Centro-Temporal Spikes (BECTS)

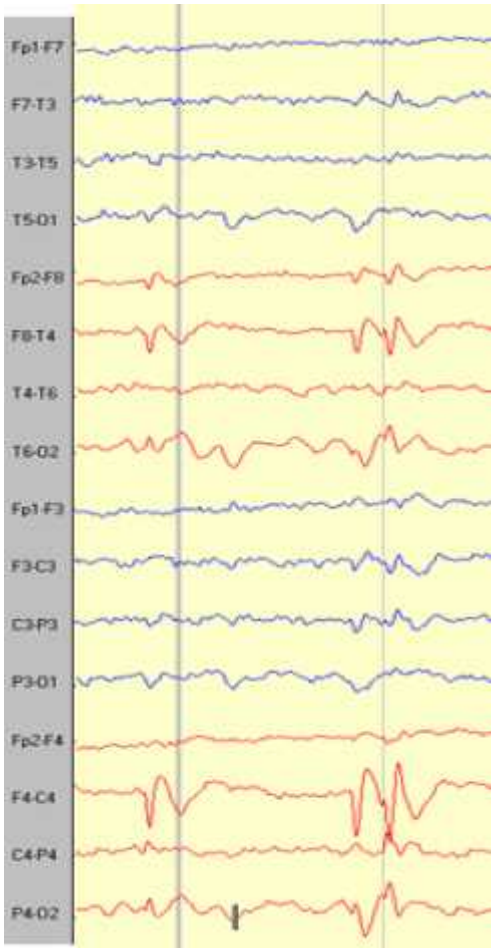
A 25 year-old man had seizures with face twitching when falling asleep at ages 9, 10 and 11 years; none since. EEG at age 9 years demonstrated centro-temporal spikes.



Benign Epilepsy with Centro-Temporal Spikes (BECTS)

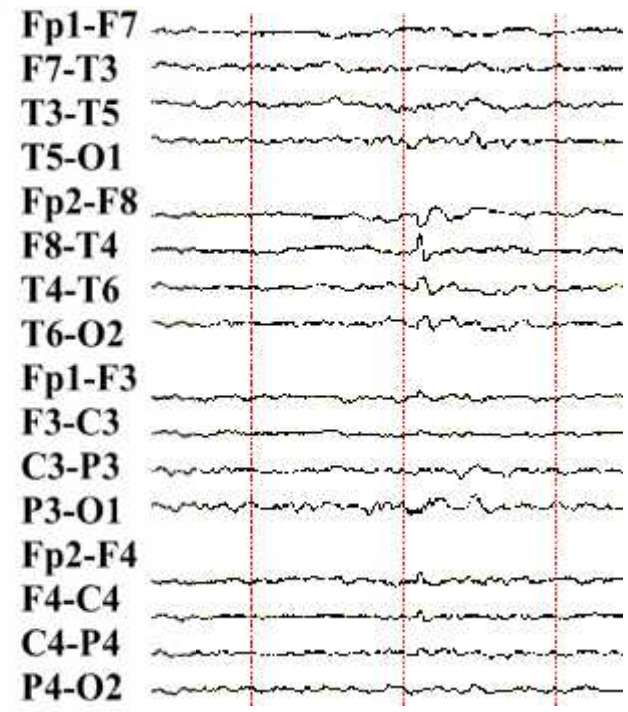
A 25 year-old man had seizures with face twitching when falling asleep at ages 9, 10 and 11 years; none since. EEG at age 9 years demonstrated centro-temporal spikes.

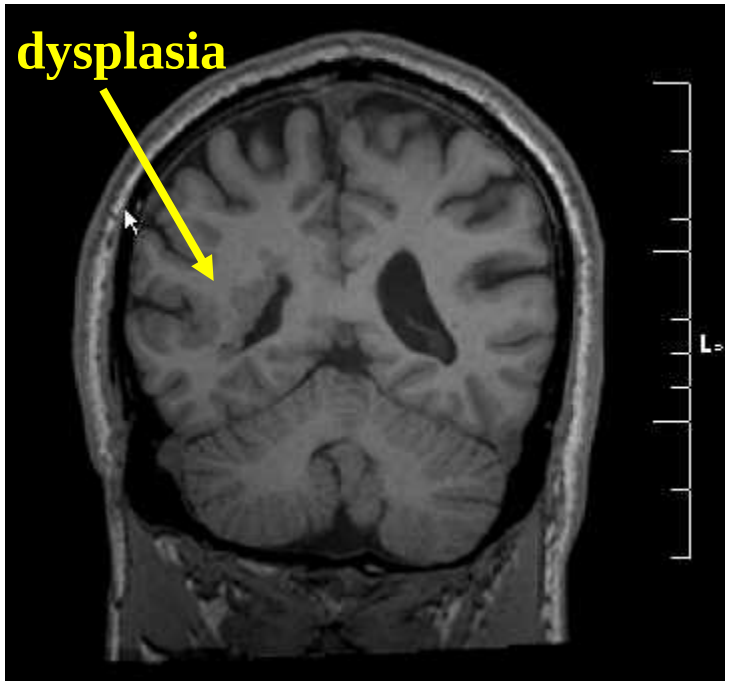
Comment: For this young man, epilepsy is no longer present, because of passing the relevant age range of an age-dependent syndrome. The old definition has no provision for considering epilepsy to be no longer present.



HYPOTHETICAL CASE: Single Seizure & Dysplasia

A 40 year-old man had a focal seizure characterized by left hand twitching that progressed to a tonic-clonic seizure. This was his only seizure. MRI shows a probable periventricular dysplasia in the right frontal lobe and EEG shows right fronto-temporal interictal spikes.





HYPOTHETICAL CASE: Single Seizure & Dysplasia

A 40 year-old man had a focal seizure characterized by left hand twitching that progressed to a tonic-clonic seizure. This was his only seizure. MRI shows a probable periventricular dysplasia in the right frontal lobe and EEG shows right fronto-temporal interictal spikes.

Comment: Although many clinicians would reasonably treat this man with anti-seizure medications, the recurrence risk for seizures is not precisely known, and therefore epilepsy cannot yet be said to be present according to either definition. Should evidence later indicate at least a 60% risk for another seizure, then a diagnosis of epilepsy would be justified by the new definition.

HYPOTHETICAL CASE: Two Seizures Long Ago

An 85 year-old man had a focal seizure at age 6 and another at age 8 years. EEG, MRI, blood tests and family history were all unrevealing. He received anti-seizure drugs from age 8 to age 10 years, when they were discontinued. There have been no further seizures.

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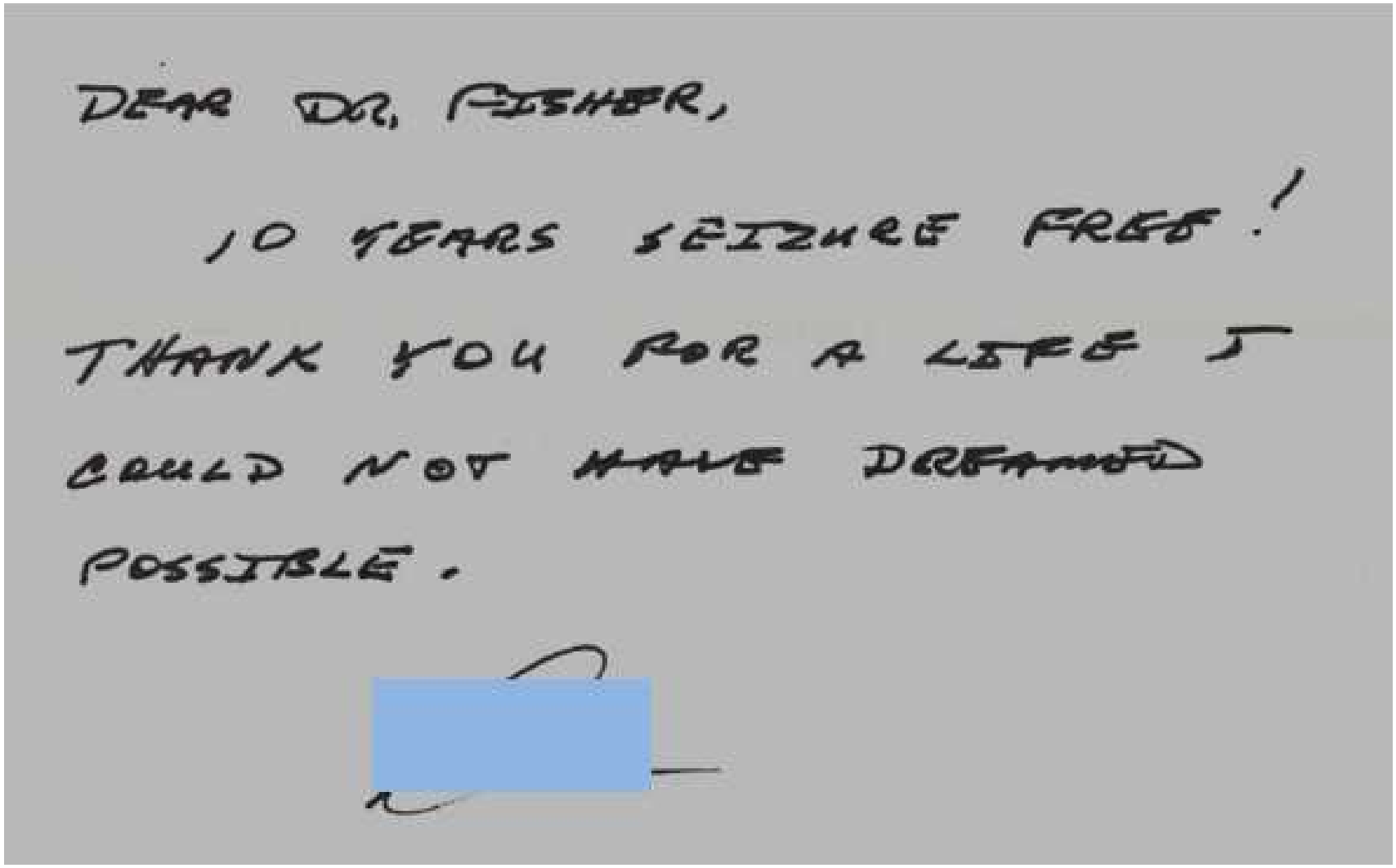
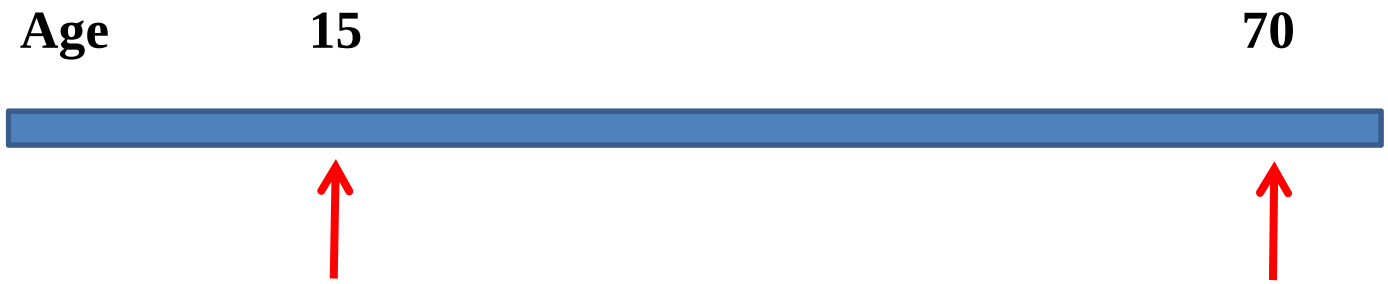
Comment: According to the new definition, epilepsy is no longer present, since he has been more than 10 years seizure-free and off seizure medication. This is not a guarantee against future seizures, but he has a right to be viewed as someone who does not currently have epilepsy.



This patient is now flying private aircraft

HYPOTHETICAL CASE: Long-Interval Seizures

A 70 year-old woman had unprovoked seizures at ages 15 and 70. EEG, MRI and family history are unremarkable.



HYPOTHETICAL CASE: Long-Interval Seizures

A 70 year-old woman had unprovoked seizures at ages 15 and 70. EEG, MRI and family history are unremarkable.

Comment: Both old and new definitions consider this woman to have epilepsy. Despite the diagnosis, many clinicians would not treat because of the infrequency of seizures. Should investigations somehow show that the causes of the two seizures were different, then epilepsy would not be considered to be present.

HYPOTHETICAL CASE: Questionable Information

A 20 year-old man has had 3 unobserved episodes over 6 months consisting of sudden fear, difficulty talking and a need to walk around. He is not aware of any memory loss during the episodes. There are no other symptoms. He has no risk factors for epilepsy and no prior known seizures.

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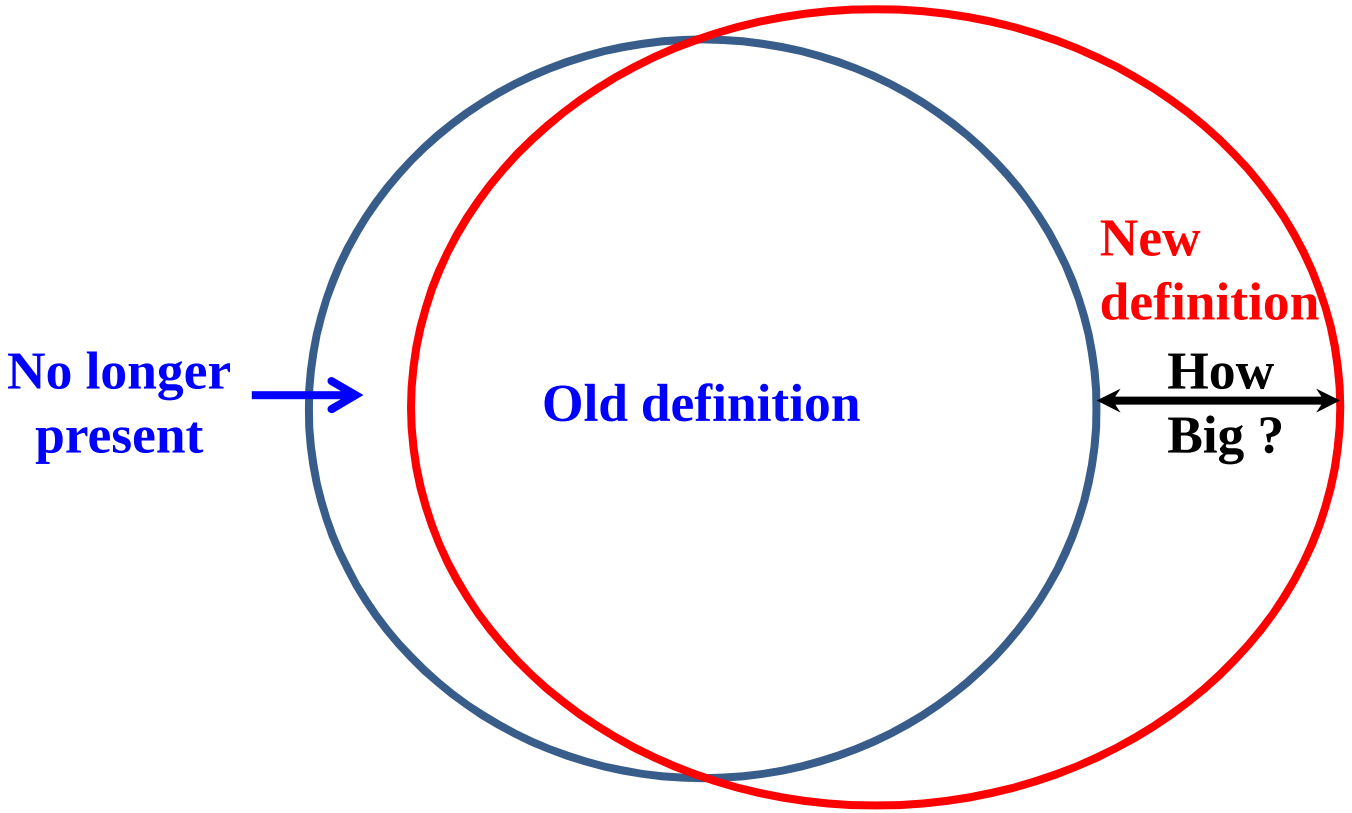
Comment: Declaring this man to have epilepsy is impossible by either the old or new definition. Focal seizures are on the differential diagnosis of his episodes, but both definitions of epilepsy require confidence that the person has had at least one seizure, rather than one of the imitators of seizures. Future discussions may define the boundaries of “possible and probable epilepsy.”


No longer present
Old definition
New definition
How Big ?

Possible Consequences

Good

Closer to clinician view
Helps reimbursement
Support for earlier diagnosis
Encourages disease-modifying therapy
Allows for epilepsy no longer present

Not so Good

May upset those diagnosed sooner
May increase stigma for some
Label of epilepsy may restrict some activities
Data on seizure recurrence is limited
Makes diagnosis more complex