ASPETTI CONTROVERSI NELLA TERAPIA ANTIEPILETTICA QUANDO INIZIARE IL TRATTAMENTO

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Definition of Epilepsy

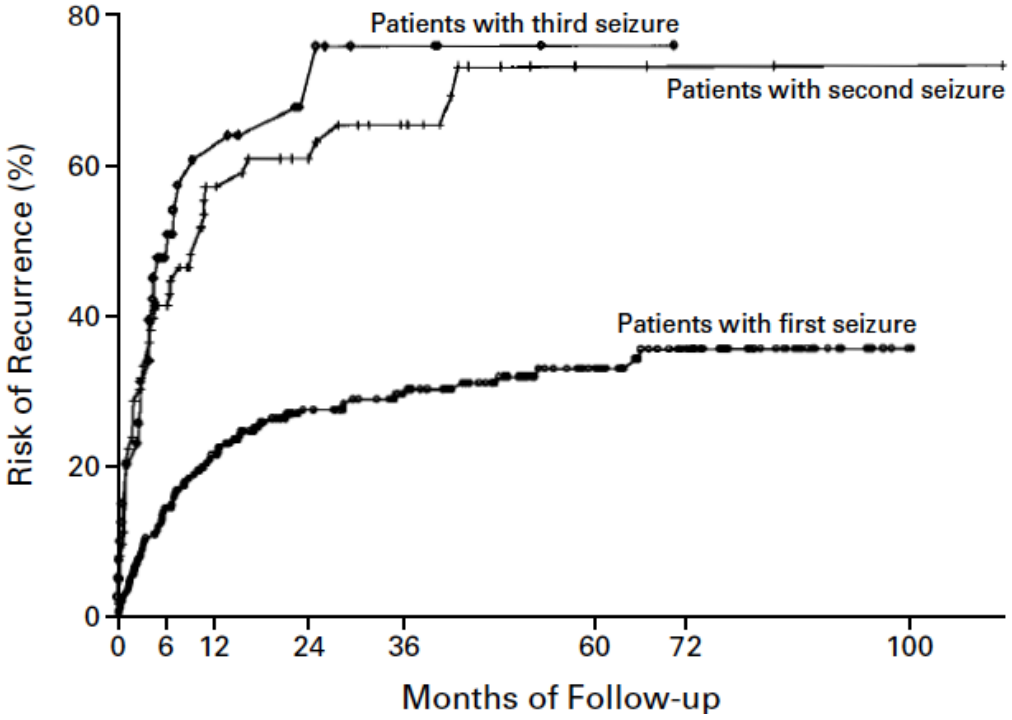
- Epilepsy is a disease of the brain defined by any of the following conditions:
  - At least **two unprovoked** (or reflex) seizures occurring more than 24 hours apart
  - **One unprovoked** (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (**at least 60%**) after two unprovoked seizures, occurring over the next 10 years
  - Diagnosis of an **epilepsy syndrome**
- Epilepsy is considered to be resolved for individuals who had an age-dependent self-limited epilepsy syndrome but who are now past the applicable age, or for those who have remained seizure-free for the last **10 years,** with no seizure medication for the last **5 years.**

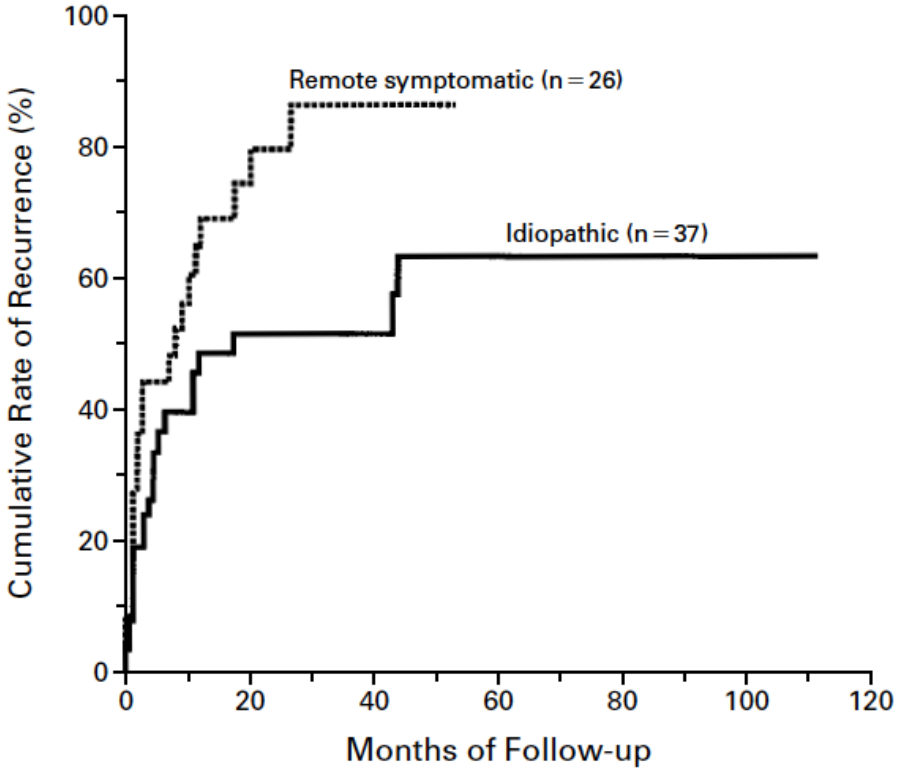
A practical clinical definition of epilepsy
Epilepsia, 55(4):475–482, 2014

RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES

W. ALLEN HAUSER, M.D., STEPHEN S. RICH, PH.D., JU R.-J. LEE, PH.D., JOHN F. ANNEGERS, PH.D., AND V. ELVING ANDERSON, PH.D.

N Engl J Med 1998;338:429-34





First seizure classification

- **Provoked immediate**
  - caused by toxin, medication, or metabolic factors
- **Acute symptomatic**
  - a seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult
- **Remote symptomatic**
  - seizure caused by preexisting brain injury
- **Seizure associated with epileptic syndrome**
  - e.g., juvenile myoclonic epilepsy
- **Unidentified**

S. Rizvi et al./Seizure 49 (2017) 46–53

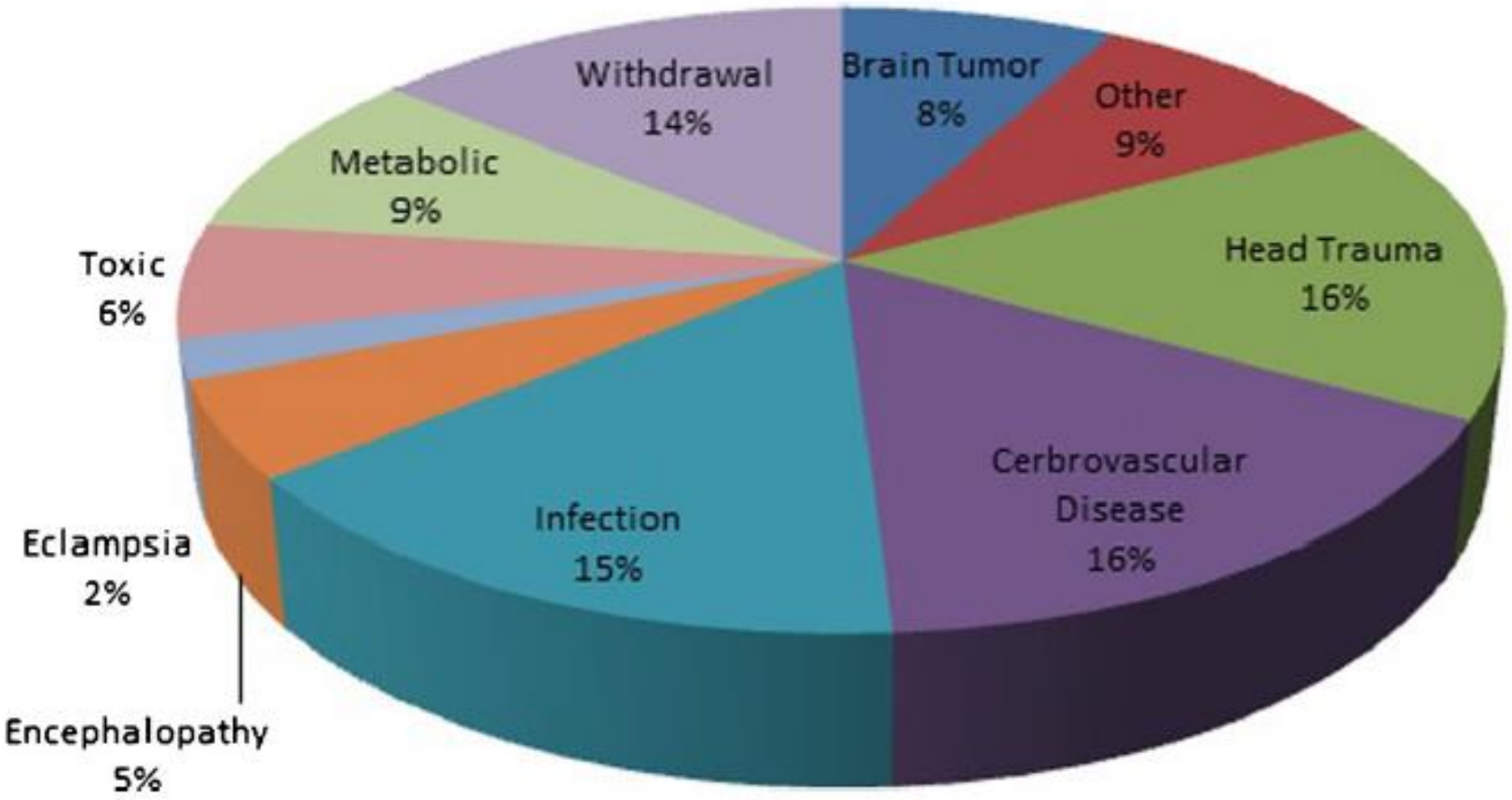
Provoked seizures

Biochemical parameter	Value
Serum glucose	<36 mg/dl (2.0 mM) or >450 mg/dl (25 mM) associated with ketoacidosis (whether or not there is long-standing diabetes)
Serum sodium	<115 mg/dl (<5 mM)
Serum calcium	<5.0 mg/dl (<1.2 mM)
Serum magnesium	<0.8 mg/dl (<0.3 mM)
Urea nitrogen	<100 mg/dl (>35.7 mM)
Creatinine	>10.0 mg/dl (>884 μM)

- Alcohol withdrawal seizures
  - abrupt cessation
  - heavy alcohol use

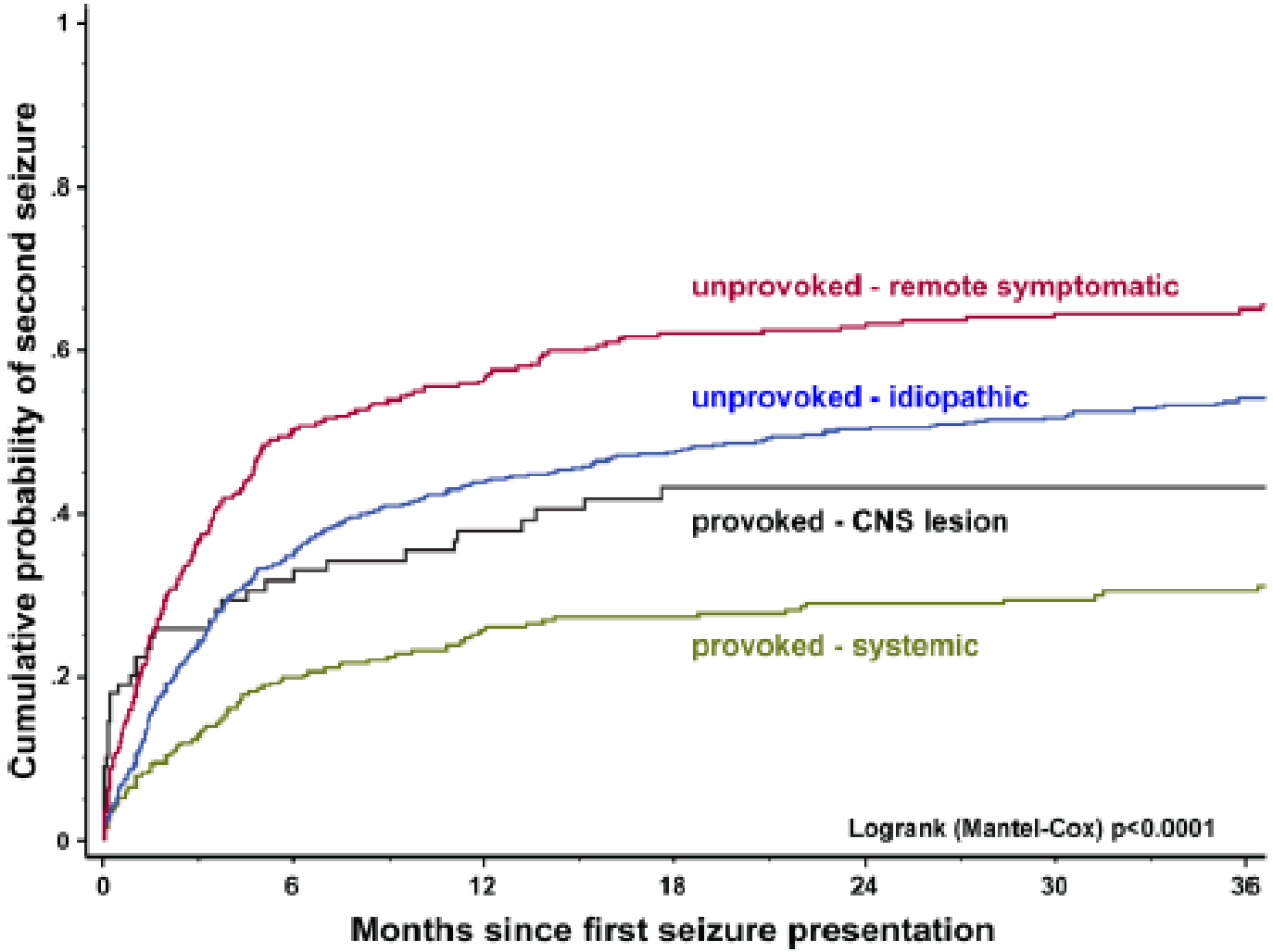
NO ANTI-EPILEPTIC TREATMENT!

Symptomatic seizures aetiology



Epilepsia. 1995;36(4):327–33

Seizure recurrence according to aetiological subgroup of first seizure.



Brown JWL, *et al*. *J Neurol Neurosurg Psychiatry* 2015;**86**:60–64.

Acute or Remote symptomatic seizure?

- Insult to the central nervous system that is known to increase substantially the risk for subsequent epilepsy:
  - Head trauma
    - N Engl J Med 1998;338:20-4
  - Cerebrovascular insult
    - Neurology1996;46:350-5
  - CNS infection
    - J Infect Dis 1986;154:399-408
  - Encephalopathy from birth or cerebral palsy
    - Dev Med Child Neurol 1986;28:Suppl 53:36

Within 7 days → Acute

- Beyond 7 days
- Abn lab tests → Acute

Remote

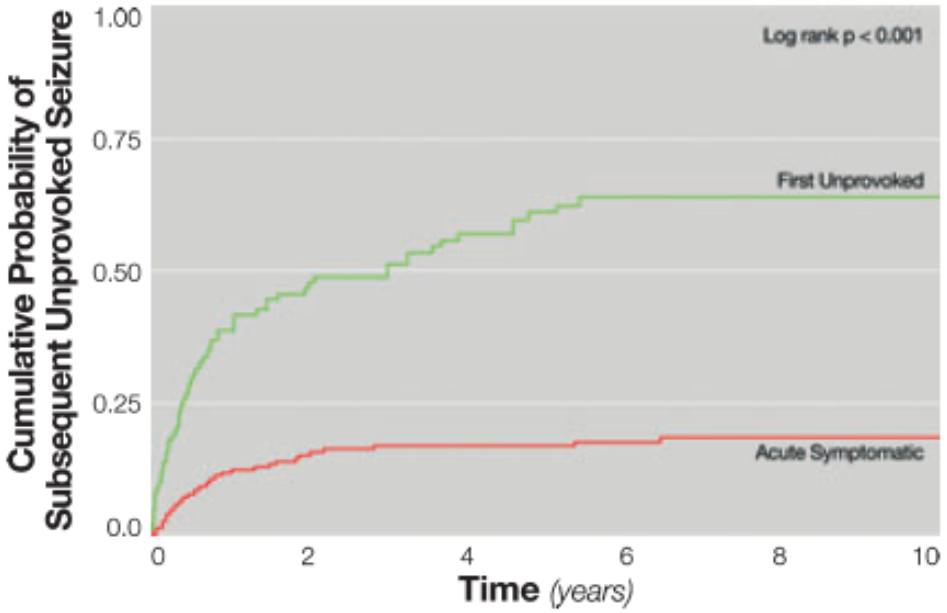
To treat or not to treat…

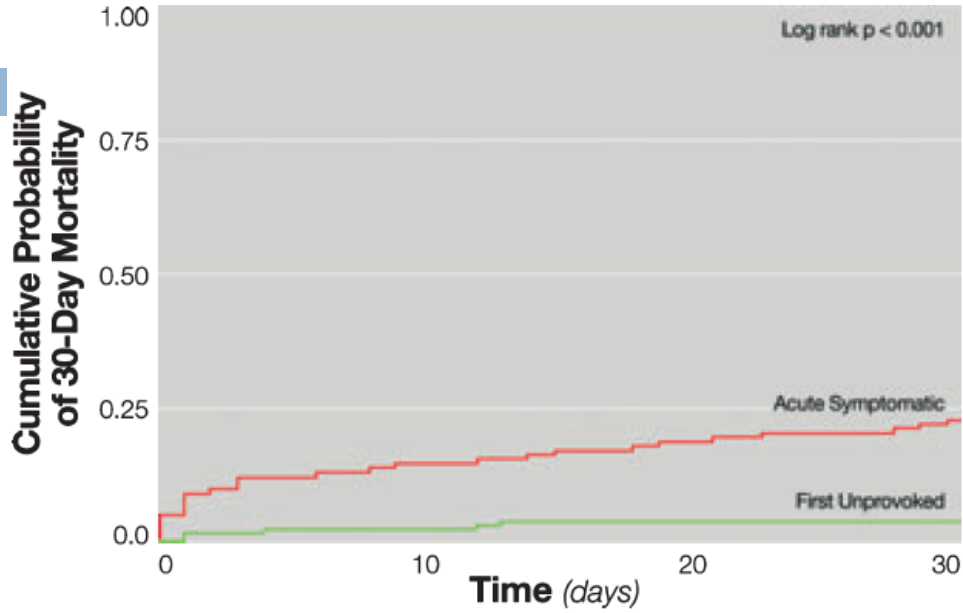
- Should we treat a first **acute** symptomatic seizure?
- Should we treat a first **remote** symptomatic seizure?

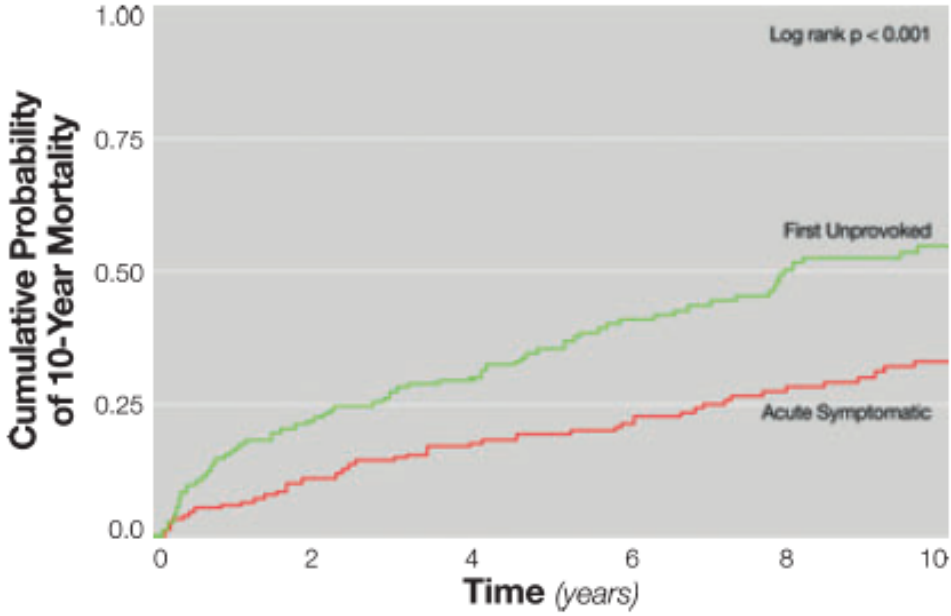
Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure

*Dale C. Hesdorffer, †Emma K. T. Benn, ‡Gregory D. Cascino, and §¶W. Allen Hauser

Epilepsia, 50(5):1102–1108, 2009







- Acute sympt seizure due to <u>static brain lesion</u>
  - No treatment

To treat or not to treat…

- Should we treat a first **acute** symptomatic seizure?
  - **NO!**
- Should we treat a first **remote** symptomatic seizure?
  - **YES!**

Evidence-based guideline: Management of an unprovoked first seizure in adults

Neurology® 2015;84:1705-1713

- Risk of **seizure recurrence** within 2 ys → 21- 45%
- **Increased risk** of seizure recurrence
  - Brain insult (stroke, trauma)
  - Brain-imaging significant abnormalities
  - EEG epileptiform abnormalities
  - Nocturnal seizure
- **Immediate AEDs treatment** may not improve QOL and is unlikely to improve the **prognosis** for sustained seizure remission
- 7 – 31% risk of mild & reversible adverse events

Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors : Report of the Quality Standards Subcommittee of the American Academy of Neurology

M.J. Glantz, B.F. Cole, P.A. Forsyth, et al.

Neurology 2000;54;1886

- In patients with newly diagnosed brain tumors, anticonvulsant medications are **not effective** in preventing first seizures.
  - **Prophylactic anticonvulsants** should not be used routinely in patients with newly diagnosed brain tumors.

- In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is **appropriate**.

Epilepsy and brain tumors

Incidence and risk factors of epilepsy across brain tumor types

Tumor type	Approximate incidence of seizures	Risk factor for seizures	References
Glioneuronal tumors	70–80%	Frontotemporal, insular	Aronica et al. (2001); Luyken et al. (2003); Southwell et al. (2012)
Low-grade gliomas	60–75%	Frontotemporal, insular, superficial	Chang et al. (2008a); Pignatti et al. (2002); Recht and Glantz (2008); Lee et al. (2010); You et al. (2012); Iuchi et al. (2015)
High-grade gliomas	25–60%	WHO grade III, temporal lobe, superficial	Sheth (2002); van Breemen et al. (2007); Jacoby et al. (2008); Chaichana et al. (2009b); Sizoo et al. (2010)
Meningiomas	20–50%	Peritumoral edema	Yao (1994); Chow et al. (1995); Lieu and Howng (2000); Oberndorfer et al. (2002)
Metastases	20–35%	Melanoma, lung cancer	Oberndorfer et al. (2002); Lynam et al. (2007); Avila (2013)

WHO, World Health Organization.

Epilepsy and brain tumors

Seizure outcomes in surgery for brain tumors associated with preoperative epilepsy

Tumor type	Approximate seizure freedom rates	Seizure freedom predictors	References
Glioneuronal tumors	70–90%	Gross total resection, early surgery, absence of generalized seizures	Giulioni et al. (2005); Park et al. (2008); Chang et al. (2010); Englot et al. (2012a); Southwell et al. (2012)
Low-grade gliomas	65–80%	Gross total resection, early surgery, localized EEG, less severe epilepsy	Luyken et al. (2003); Zaatreh et al. (2003); Benifla et al. (2006); Chang et al. (2008a); Englot et al. (2011)
Meningiomas	60–80%	Less peritumoral edema	Chow et al. (1995); Lieu and Howng (2000); Chaichana et al. (2013); Fang et al. (2013); Zheng et al. (2013)

Adapted from: Curr Treat Options Neurol (2018) 20: 41

Management guidelines

Etiology	Type of seizure	Short-term AED	Long-term AED
Alcohol	Provoked	Yes, BDZ	No
Metabolic	Provoked	Maybe, if prolonged abn	No
Ischemic stroke	Acute SS	Maybe, depending on lesion	Yes, if develops remote SS
Hemorrhagic stroke	Acute SS	Maybe, depending on lesion	Yes, if develops remote SS
Subdural	Acute SS	Maybe, depending on lesion	Yes, if develops remote SS
Subarachnoid	Acute SS	Maybe, depending on lesion	Yes, if develops remote SS
Cerebral venous sinus thrombosis	Acute SS	Yes, 6-12 months	Yes, if develops remote SS
PRES	Acute SS	Yes, + treat etiology	No
Eclampsia	Acute SS	Maybe, + ev Mg & BP control	No
Trauma	Acute SS	Yes, 1 week → 3 months	Yes, if develops remote SS
CNS infection	Acute SS	Yes, + treat etiology	Yes, if develops remote SS

When to stop? …next talk!

Grazie!!!

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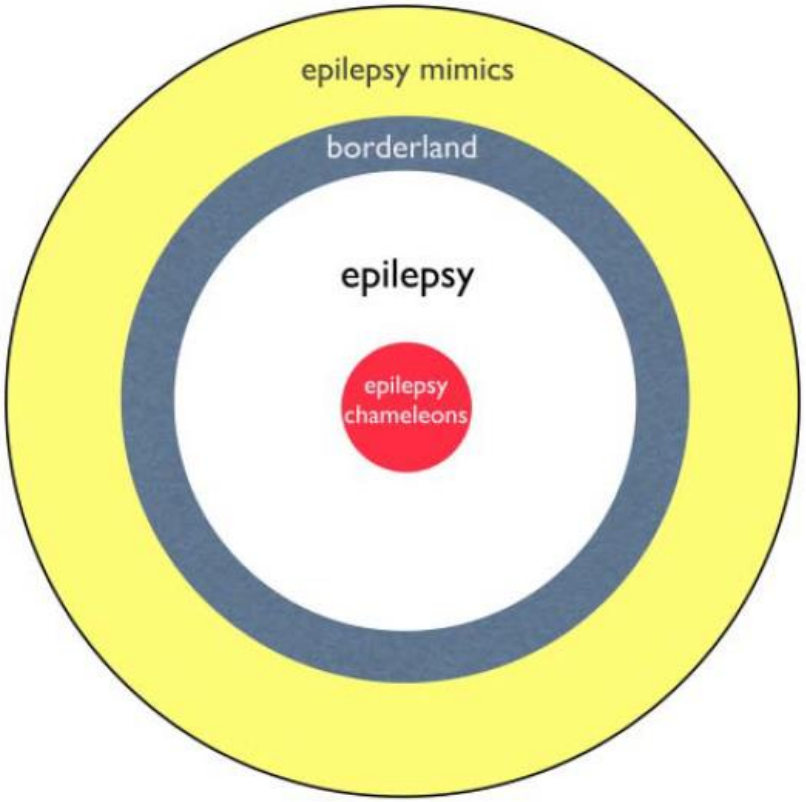
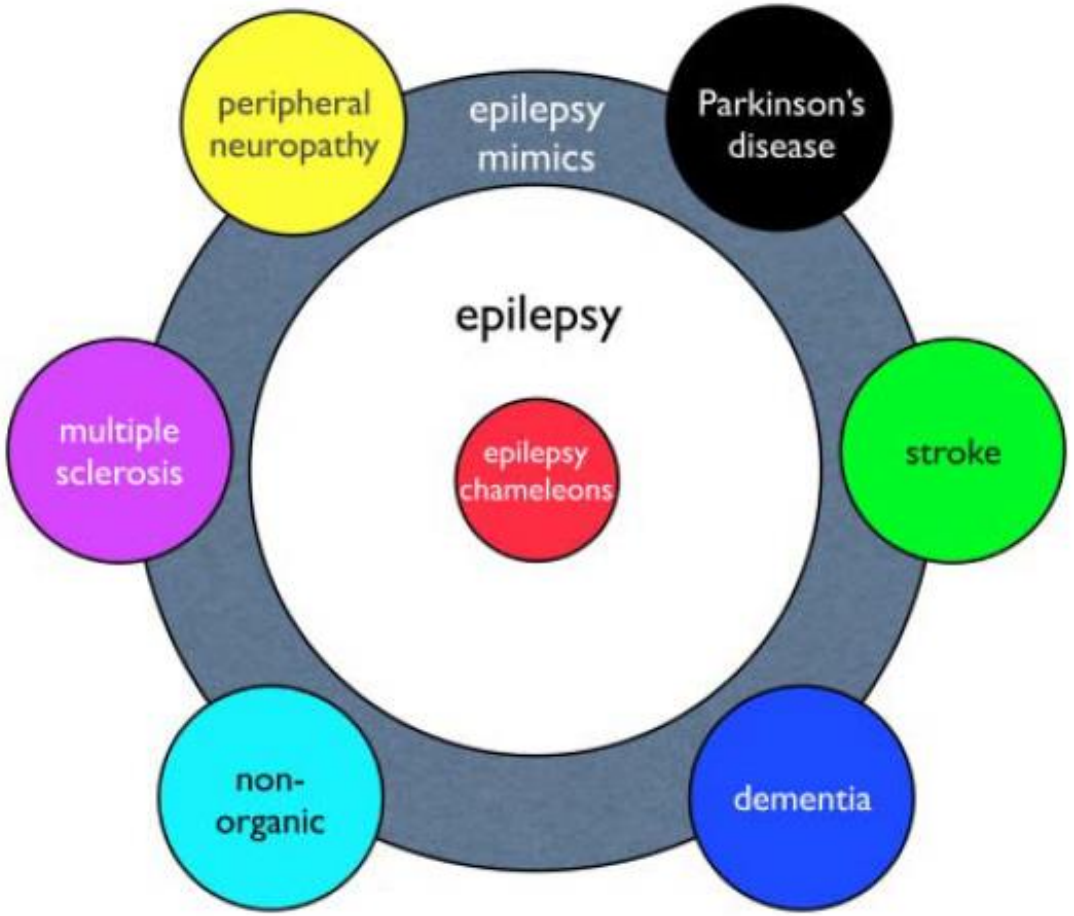
Epilepsy: mimics, borderland and chameleons

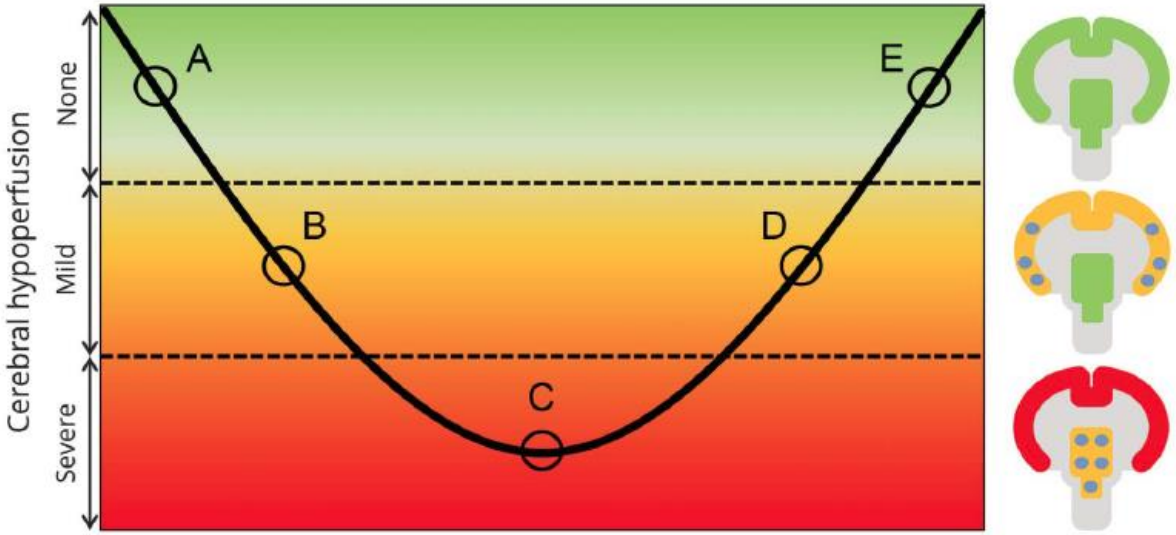
Practical Neurology 2012;**12**:299–307.





Mimics

- Syncope time course



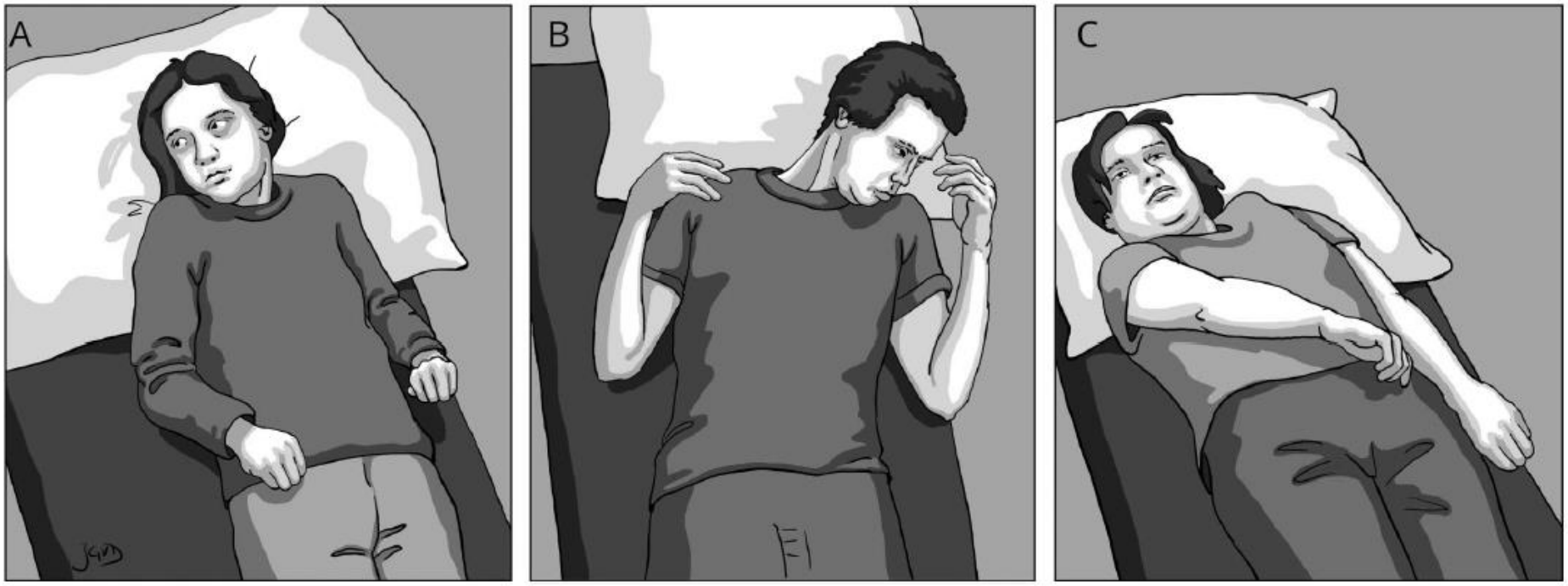
	A and E	B and D	C
Function			
EEG	Normal	Slow	Flat
Cortex	Normal	Reduced and disinhibition	Loss
Brainstem	Normal	Normal	Reduced and disinhibition
Motor phenomena	None	Myoclonic jerks	Tonic postures

- Syncope
- Reflex
  - Vasovagal, micturition, swallow, carotid sinus, orgasmic and laughing
- Cardiac
  - Arrhythmogenic
  - Elderly: scar-related ventricular tachycardia
  - Young: long QT syndrome, short QT syndrome, arrhythmogenic right ventricular cardiomyopathy
  - Structural, aortic stenosis, hypertrophic cardiomyopathy
- Orthostatic
  - Autonomic failure
- Psychogenic non-epileptic attack disorder
  - Panic disorder (especially in people with epilepsy)
  - Dissociative
  - Factitious and malingering
- Sleep disorders
  - Narcolepsy syndrome and cataplexy
  - Parasomnias (see Borderland of epilepsy section)
- Paroxysmal symptoms of structural brain disease
  - Multiple sclerosis
  - Tumour, eg, brainstem glioma
- Vascular
  - Migraine (hemiparetic, occipital, 'basilar artery')
  - Shaking transient ischaemic attack (critical bilateral stenosis)
  - Subclavian steal syndrome
  - Moyamoya (combination of TIA and seizures)
  - *Not* vertebrobasilar insufficiency
- Hypoglycaemia
  - Behaviour disturbance
  - Hemiparesis
- Movement disorder
  - Paroxysmal kinesigenic dystonia/dyskinesia
  - Myoclonus following hypoxia
- Hydrocephalus
  - Colloid cyst
  - Chiari malformation
- Drop attacks
  - Postural instability
  - Psychogenic

Differentiating motor phenomena in tilt-induced syncope and convulsive seizures

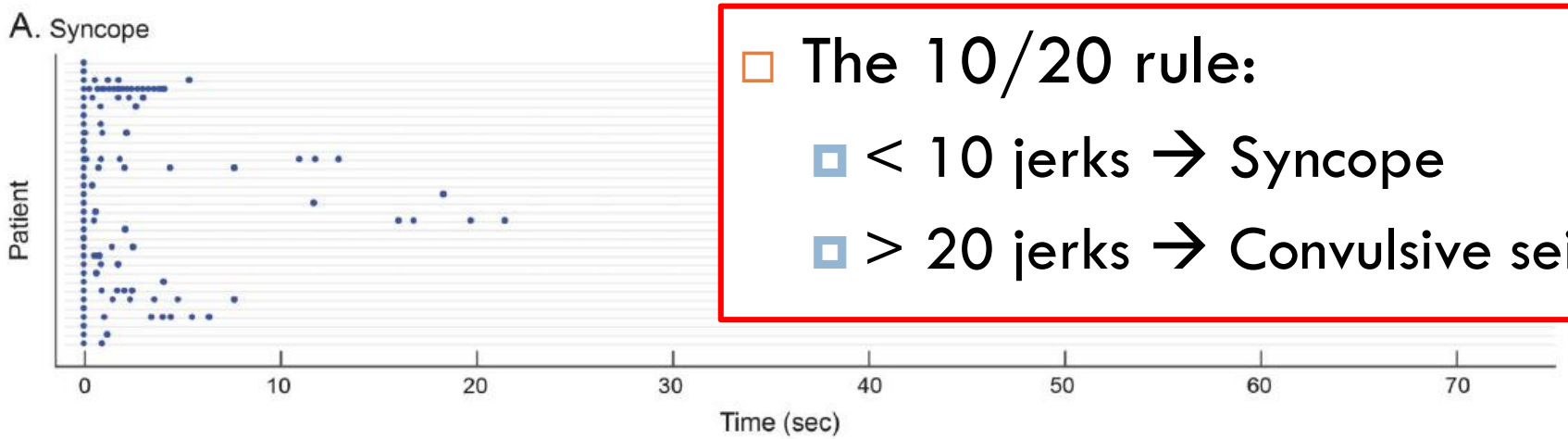
Neurology® 2018;90:e1339-e1346.

Figure 2 Illustration of flexion and extension postures in tilt-induced syncope

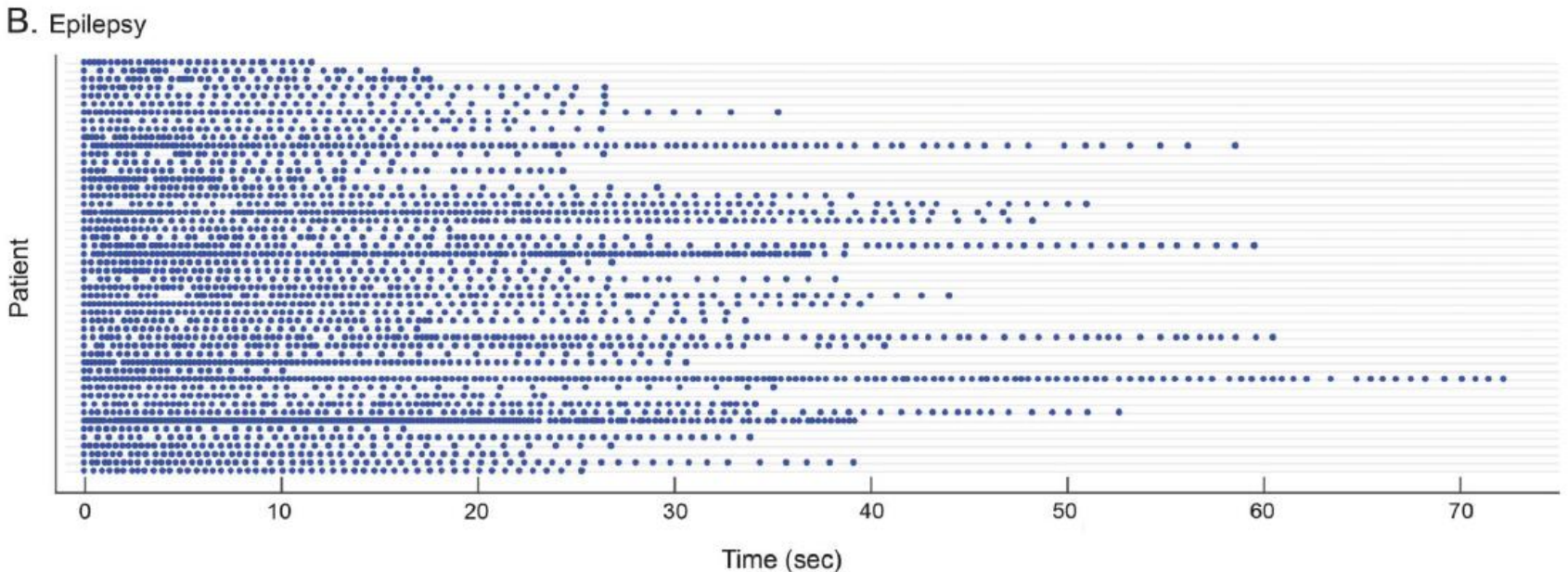


Differentiating motor phenomena in tilt-induced syncope and convulsive seizures

Neurology® 2018;90:e1339-e1346.



- The 10/20 rule:
  - < 10 jerks → Syncope
  - > 20 jerks → Convulsive seizure



Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: A staged approach

Epilepsia, 54(11):2005–2018, 2013

Signs that favor PNES	Evidence from primary studies	Sensitivity (%) for PNES	Specificity (%) for PNES
Long duration	Good	–	–
Fluctuating course	Good	69 (events)	96
Asynchronous movements	Good (frontal lobe partial seizures excluded)	47–88 (patients)	96–100
		44–96 (events)	93–96
		9–56 (patients)	93–100
Pelvic thrusting	Good (frontal lobe partial seizures excluded)	1–31 (events)	96–100
		7.4–44 (patients)	92–100
Side to side head or body movement	Good (convulsive events only)	25–63 (events)	96–100
		15–36 (patients)	92–100
Closed eyes	Good	34–88 (events)	74–100
		52–96 (patients)	97
Ictal crying	Good	13–14 (events)	100
		3.7–37 (patients)	100
Memory recall	Good	63 (events)	96
		77–88 (patients)	90

Signs that favor ES	Evidence from primary studies	Sensitivity for ES	Specificity for ES
Occurrence from EEG-confirmed sleep	Good	31–59 (events)	100
		–	–
Postictal confusion	Good	61–100 (events)	88
		67 (patients)	84
Stertorous breathing	Good (convulsive events only)	61–91 (events)	100
		–	–

Other signs	Evidence from primary studies
Gradual onset	Insufficient
Nonstereotyped events	Insufficient
Flailing or thrashing movements	Insufficient
Opisthotonus "arc en cercle"	Insufficient
Tongue biting	Insufficient
Urinary incontinence	Insufficient

Acute symptomatic seizures

Practical Neurology 2012;**12**:154–165.

Rob Powell,[1] Duncan James McLauchlan[2]

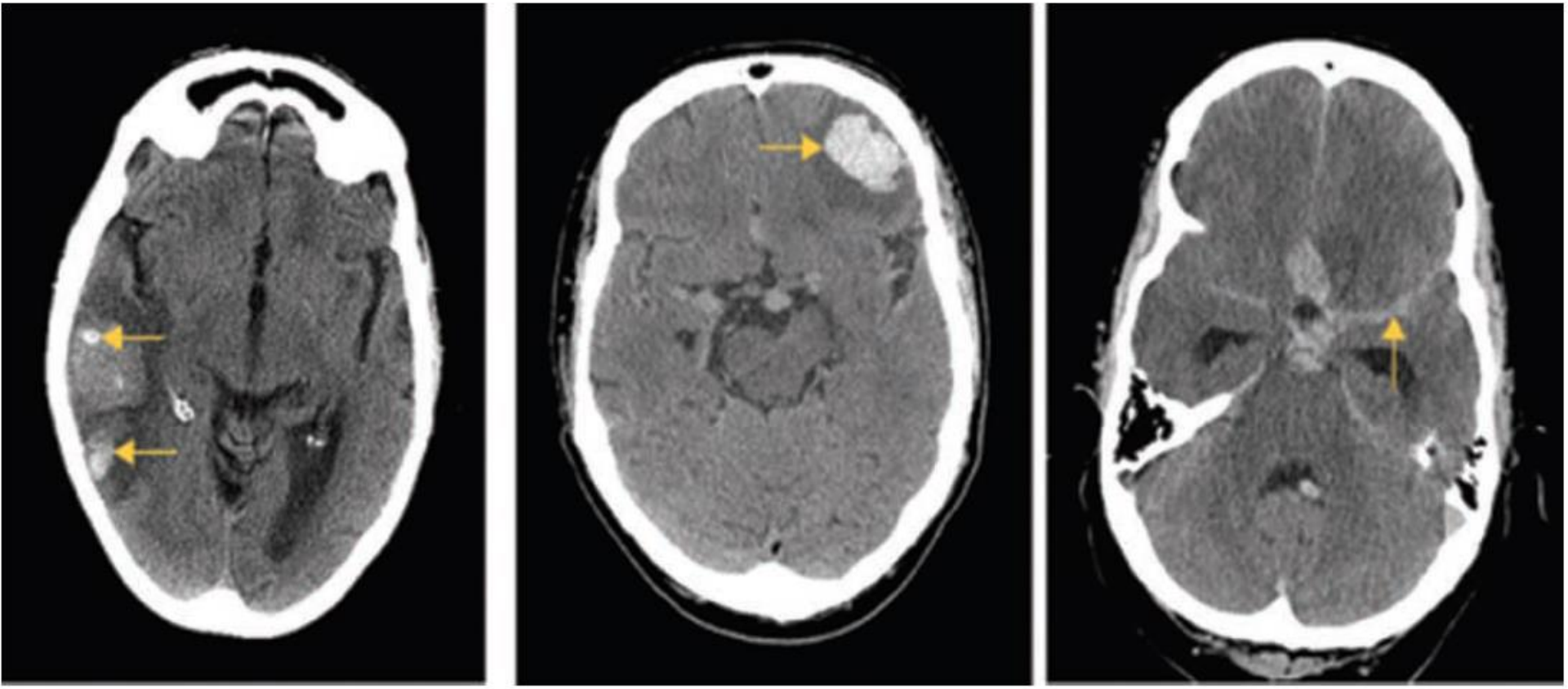
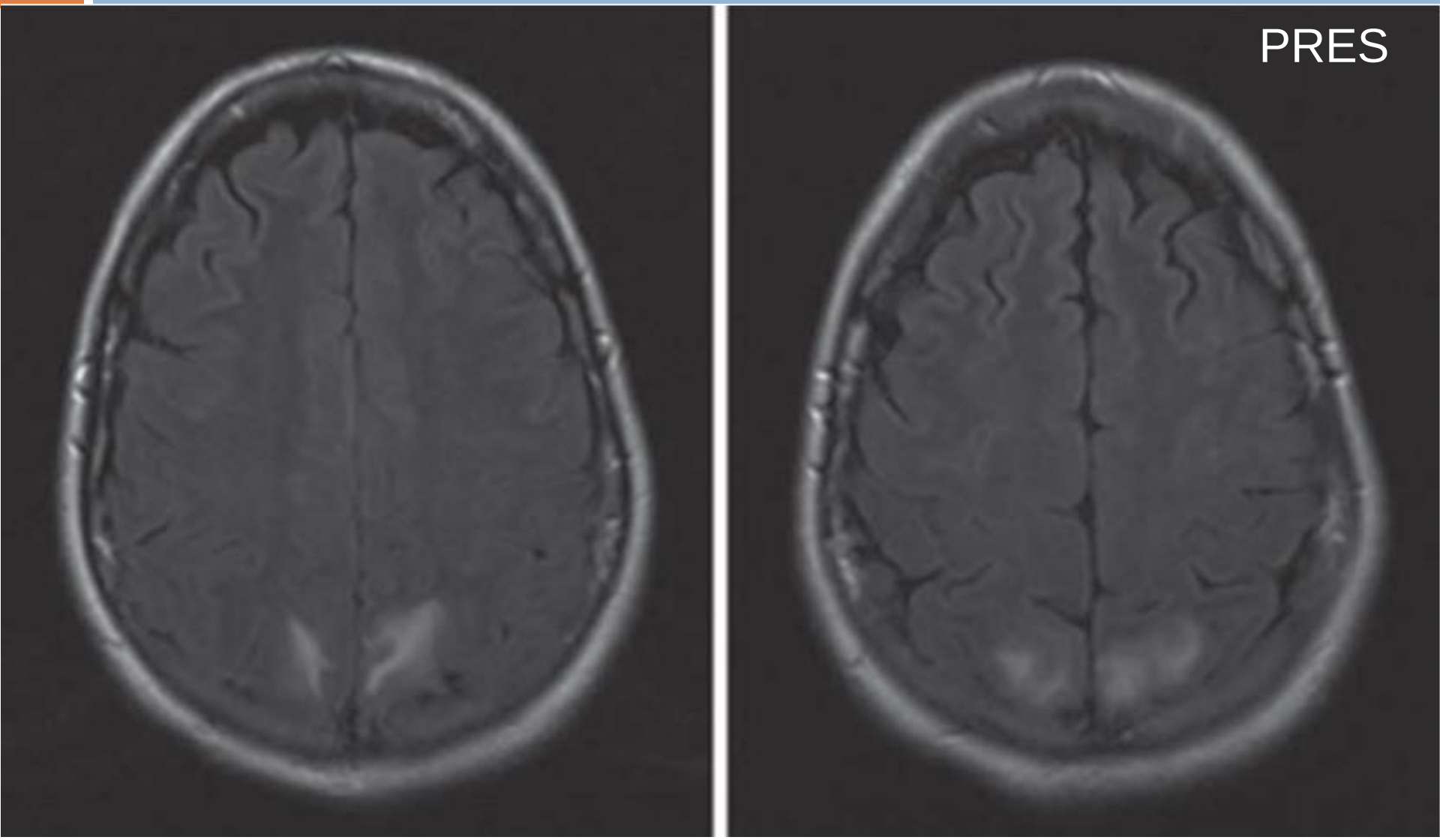


Figure 1 CT scan of head showing transverse sinus thrombosis causing venous infarctions and haemorrhagic transformation with intracerebral and subarachnoid haemorrhage.

Acute symptomatic seizures

Practical Neurology 2012;**12**:154–165.

Rob Powell,[1] Duncan James McLauchlan[2]



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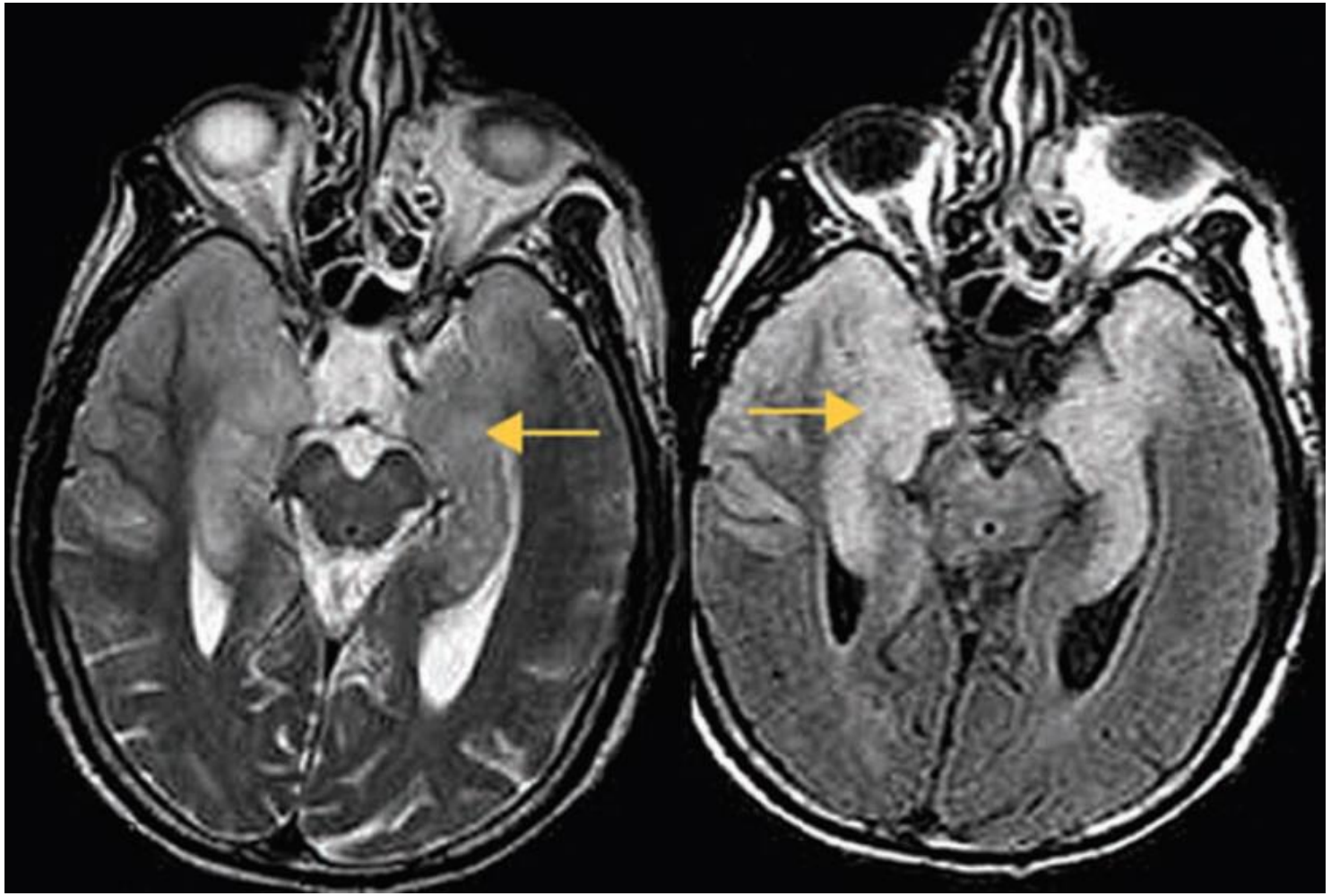
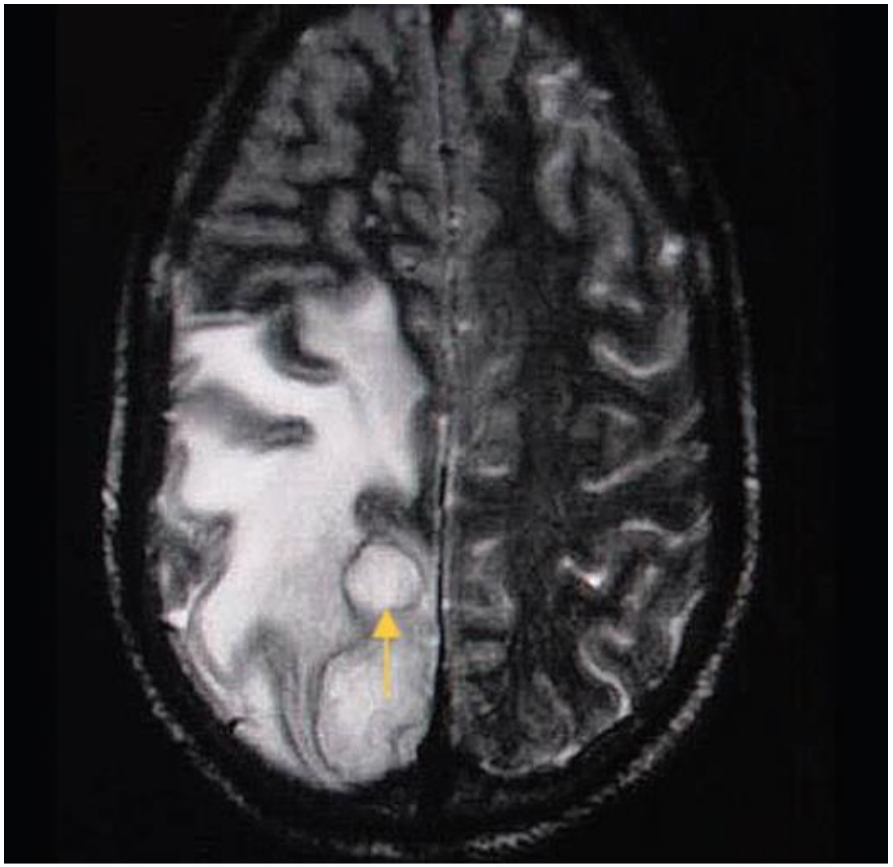


VIRAL ENCEPHALITIS

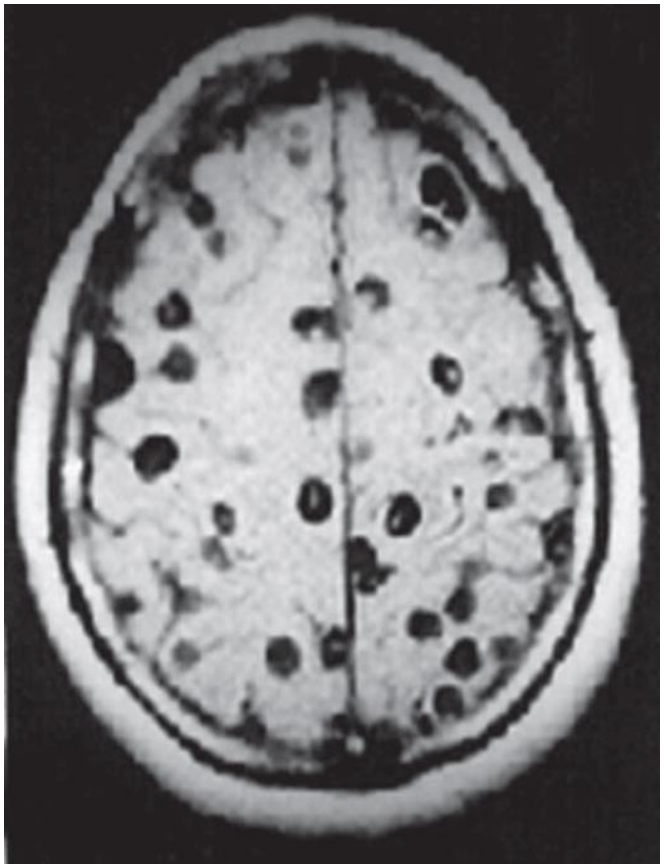
Acute symptomatic seizures

Practical Neurology 2012;**12**:154–165.

Rob Powell,[1] Duncan James McLauchlan[2]



Cerebral abscess + oedema

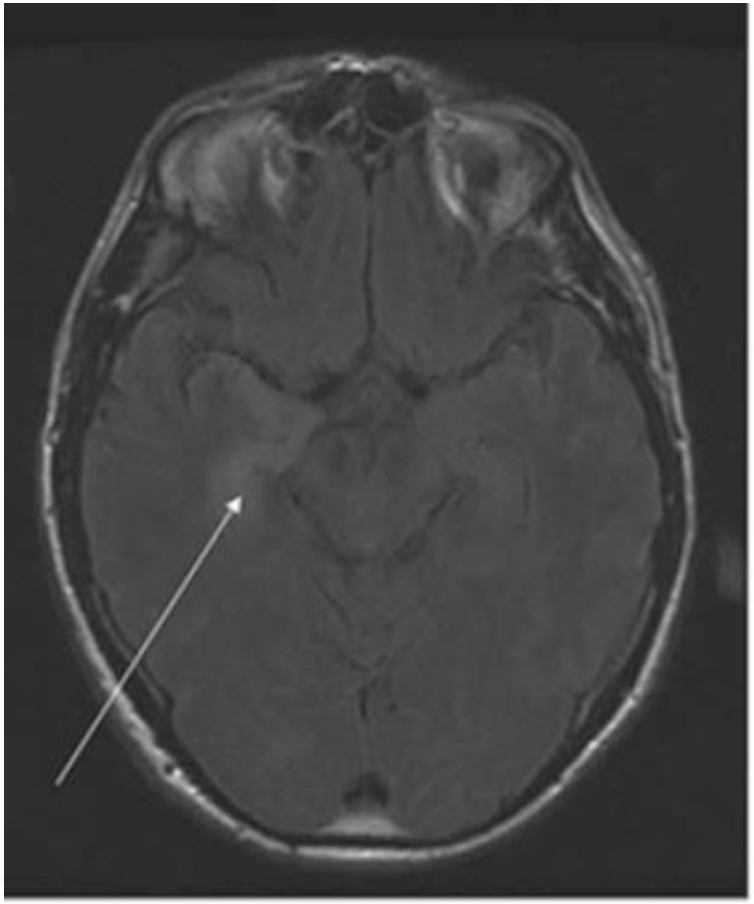


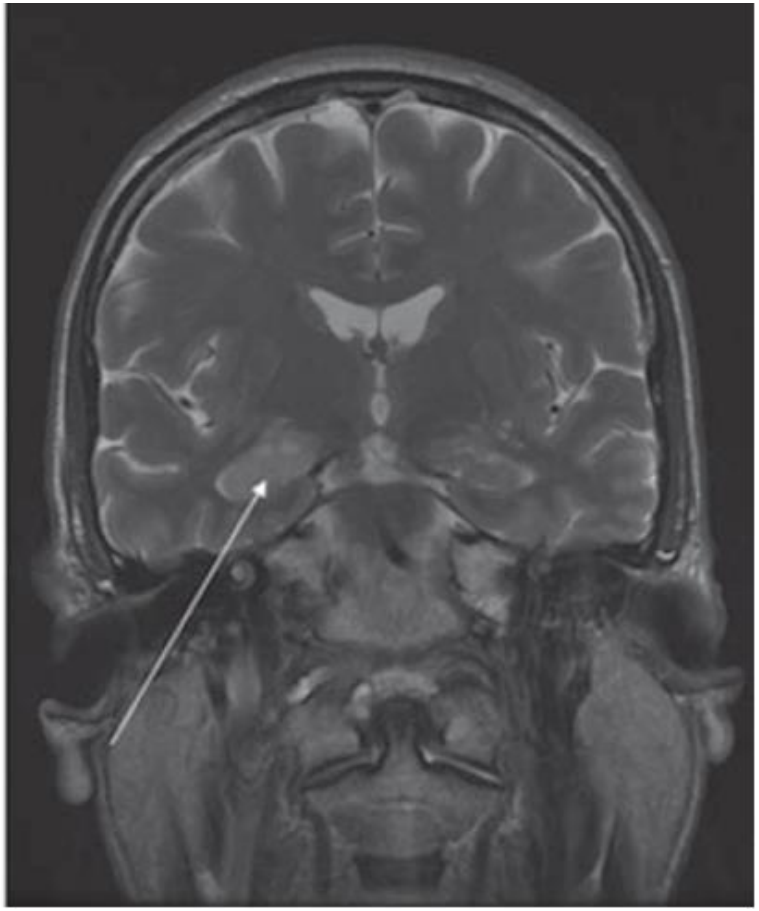
Neurocysticercosis.

Acute symptomatic seizures

Practical Neurology 2012;**12**:154–165.

Rob Powell,[1] Duncan James McLauchlan[2]





limbic encephalitis and anti-voltage-gated potassium channel antibodies