EST 30th ANNIVERSARY ANNUAL MEETING

The "First Seizure" Dilemma – To Treat or Not to Treat

Sattawut Wongwiangjunt, M.D.

Division of Neurology, Siriraj Hospital, Mahidol University

When to start ASM?

Diagnosis of epilepsy

1. ≥ 2 unprovoked (or reflex) SZs occurring >24 hours apart

Fisher et al. Epilepsia 2014

What if?

A 50-year-old man presented with unprovoked GTC SZ
He had history of seizure when he was 7 years old.
Would you diagnose this patient EPILEPSY?

No clear time interval

When to start ASM?

Diagnosis of epilepsy

1. ≥ 2 unprovoked (or reflex) SZs occurring >24 hours apart
2. 1 unprovoked (or reflex) SZ with probability of further SZs (>60%) over the next 10 yr
3. Diagnosis of epileptic syndrome

Similar to general recurrent risk after 2 unprovoked SZs

Fisher et al. Epilepsia 2014

SPECIAL ARTICLE

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

21-45% (36%)

				Seizure recurrences at various times, n (%)								
Ref.	Class	Age, y	No.	Treated	1 mo	3 mo	6 mo	1 y	2 y	3 y	5 y	>5 y
10, 11	I	70% >19	238	164 (69)	—	—	—	38 (16)	50 (21)	60 (29)	70 (34)	81 (39)
12, 13	I	72% >16	397	204 (51)	24 (6)	58 (15)	75 (19)	98 (25)	111 (28)	—	—	—
17	II	≥16	147	62 (42)	—	—	39 (27)	50 (34)	60 (41)	61 (41)	—	—
18	II	Mean >20	76	36 (47)	2 (3)	18 (24)	20 (26)	22 (29)	—	—	—	—
16	II	≥16	306	41 (13)		55 (18)	79 (26)	111 (36)	136 (44)	144 (47)	—	—
19	II	75% >15	424	?	38 (9)	89 (21)	127 (30)	153 (36)	191 (45)	204 (48)	237 (56)	244 (58)
20	II	14-91	497	127 (26)	—		—	191 (38)	—	—	—	—
15	II	60% >20	812	404 (50)	—		179 (22)	—	288 (35)	—	378 (46)	398 (49)
21	II	≥16	228	113 (50)	—	—	—	68 (30)	—	—	—	—
22	II	18-50	87	45 (52)	—		—	30 (34)	37 (43)	39 (45)	—	—
Total			3,212	1,196 (43)	64 (7)	220 (18)	519 (24)	761 (32)	873 (36)	508 (42)	685 (46)	723 (49)

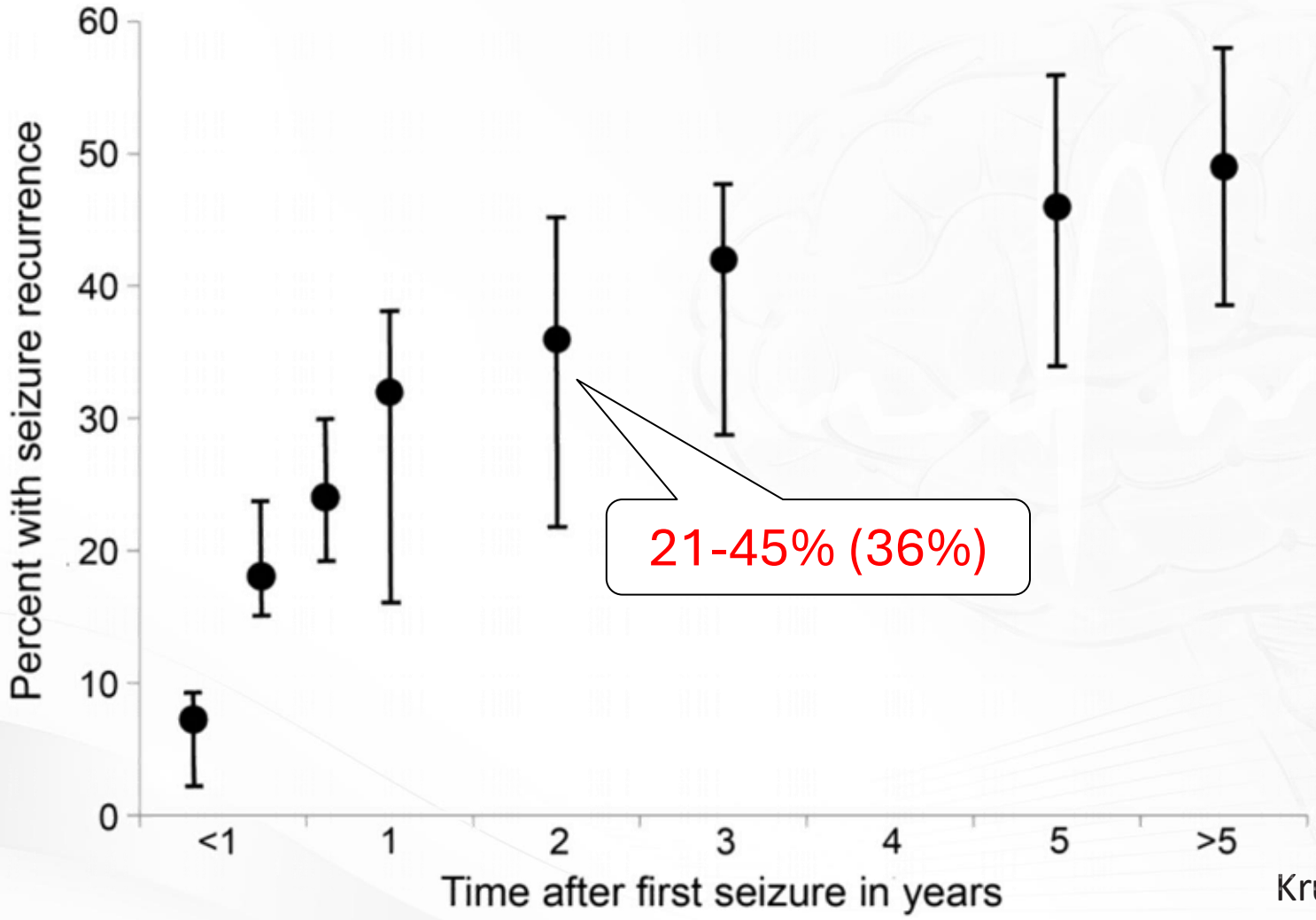
Krumholz et al. Neurology 2015

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

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



Krumholz et al. Neurology 2015

SPECIAL ARTICLE

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

Management → What to consider?

1. Short-term risk for a seizure recurrence
2. Longer-term potential for seizure remission

3. Adverse effects

Krumholz et al. Neurology 2015

SPECIAL ARTICLE

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

Management → What to consider?

1. **<u>Short-term risk for a seizure recurrence</u>**
2. Longer-term potential for seizure remission

3. Adverse effects

Krumholz et al. Neurology 2015

EST 30th ANN ANN

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

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

Short-term

Table 2 Rates for short-term (1 and 2 years) seizure recurrence after an unprovoked first seizure in adults as related to immediate antiepileptic drug treatment (Class I and II studies)

Ref.	Class	No.	Treated, n (%)	Recur. rate treated, n (%)	Recur. rate untreated, n (%)	Length of follow-up, y
12-14	I	397	204 (51)	36 (18)[a]	75 (39)	2
18	II	76	36 (47)	4 (11)[a]	18 (45)	1
15	II	812	404 (50)	129 (32)	159 (39)	2
21	II	228	113 (50)	5 (4)[a]	63 (55)	1
22	II	87	45 (52)	9 (20)[a]	28 (66)	2
Total		1,600	804 (50)	183 (23)	343 (43)	1 or 2

Krumholz et al. Neurology 2015

Treat 14 pts with a single seizure

in order to prevent a single seizure recurrence within the first 2 years.

Epilepsia, 49(Suppl. 1):26–28, 2008

EST 30th ANNIVERSARY ANNUAL MEETING

Received: 6 September 2025 | Accepted: 17 March 2026

DOI: 10.1002/epd2.70234

Epileptic Disorders

ORIGINAL ARTICLE

The second unprovoked seizure in a cohort of treated patients with a first unprovoked seizure

Revital Gandelman-Marton[1,2] | Jacques Theitler[1,2]

TABLE 2 Types of ASMs at first and last observations.

	First observation	Last observation[a]
LEV	35 (58.3)	31 (51.7)
PHT	10 (16.7)	2 (3.3)
CBZ	5 (8.3)	3 (5)
VPA	2 (3.3)	3 (5)
GBP	3 (5)	3 (5)
LTG	1 (1.7)	5 (8.3)
PRM	–	1 (1.7)
LEV + LCS	1 (1.7)	3 (5)
LEV + VPA	–	1 (1.8)
LEV + LTG	–	2 (3.3)
VPA + LTG		1 (1.7)
PHT + LTG	3 (5)	–
CBZ + LTG	–	2 (3.3)

- 2nd unprovoked seizure occurred in 43% (24/60)
- 75% of the recurrences occurred at 3 years.
- Risks higher in younger (32.9 vs. 46.9 years) (p = 0.010) and more likely to be women (64% vs. 28.6%) (p = 0.009)
- Women and younger patients may deserve closer monitoring following a 1st unprovoked seizure

SPECIAL ARTICLE

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

Management → What to consider?

1. Short-term risk for a seizure recurrence
2. **Longer-term potential for seizure remission**

3. Adverse effects

Krumholz et al. Neurology 2015

SPECIAL ARTICLE

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

Long-term

Rates of 2-year seizure remission over the longer term (>3 years), comparing immediate with deferred antiepileptic drug treatment of an unprovoked first seizure in adults (Class I and II studies)

Ref.	Class	No.	Immediate treatment, n (%)	Remission, immediate treatment, n (%)	Remission, deferred treatment, n (%)	Length of follow-up
12-14	I	419	215 (51)	174 (81), NS	159 (78)	More than 3 y[a]
15	II	812	404 (50)	372 (92), NS	375 (92)	5 y[b]
Total		1,231	619 (50)	546 (88)	534 (87)	

Krumholz et al. Neurology 2015

“ASMs are symptomatic treatments,

not disease-modifying or antiepileptogenic therapies.”

Immediate treatment buys time and safety over the first 1–2 years, but withholding medication until a 2nd seizure does not compromise the patient's ultimate chance of long-term seizure freedom."

Guidelines and epilepsy practice: Antiseizure medication initiation following an unprovoked first seizure in adults

Shir Levi-Abayo [a], Shimon Ben-Shabat [a], Revital Gandelman-Marton [b,c,*]

- **Objective:** Evaluated the translation and impact of the 2015 AAN/AES Practice Guideline into real-world clinical decision-making
- ASMs were initiated in **100% of admitted patients post-guideline publication** (compared to 86% pre-guideline).
- In pre-guideline real-world practice, decisions to start treatment were significantly influenced by **epileptiform discharges on EEG**.
- Ensuring that clinicians consistently integrate:
  - structural neuroimaging
  - remote symptomatic histories
  - EEG findings when calculating recurrence risk.

S. Levi-Abayo, et al. Epilepsy Research 200 (2024) 107304

SPECIAL ARTICLE

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

Management → What to consider?

1. Short-term risk for a seizure recurrence
2. Longer-term potential for seizure remission

3. **<u>Adverse effects</u>**

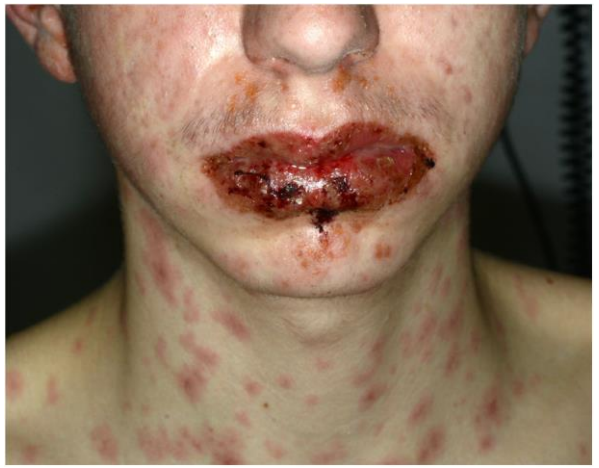
Krumholz et al. Neurology 2015

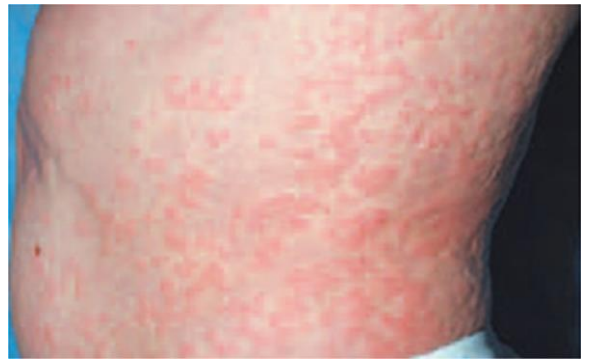
Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial

A Marson, A Jacoby, A Johnson, L Kim, C Gamble, D Chadwick, on behalf of the Medical Research Council MESS Study Group*

	Immediate treatment (n=722)	Deferred treatment (n=721)	Total
No follow-up	37	26	63
None reported	415 (61%)	481 (69%)	896 (65%)
At least one reported	270 (39%)	214 (31%)	484 (35%)
Depression, anxiety	40	31	71
Dizziness, unsteadiness	37	32	69
Gastrointestinal symptoms	41	24	65
Tiredness, drowsiness	41	23	64
Headache	37	13	50
Injury, scalds	28	22	50
Rash, acne	31	14	45
Surgery	21	21	42
Chest pain, myocardial infarction	21	21	42
Impaired memory, concentration	19	15	34
Weight gain, increased appetite	14	19	33
Behaviour problem	20	12	32
Tremor	17	6	23

Table 3: **Patients reporting adverse events at any follow-up**





Lancet 2005; 365: 2007-13

Risk of rash from ASMs

High risk	Moderate risk	Low risk
PHT (10%) CBZ (8.7%) LTG (6.2%)	PB OXC	VPA TPM LEV GBP VGB

CBZ and OXC: cross reactivity 30%

Arif et al. Neurology 2007

Aromatic ring AED: cross reactivity 40-80%

Hyson, Sadler. 1997 Krauss. Epilepsy Curr 2006

HLA B*1502 testing before starting CBZ

Treat the Risk, Not Just the Seizure

Ask, *"Does this patient meet the >60% recurrence threshold?"*
rather than *"Is one seizure enough to treat?"*

EST 30th ANNIVERSARY ANNUAL MEETING

- 23 studies evaluated
- 5,918 total participants (children and adults)
- Follow-up period of at least 6 months

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Review language :

Title Ab

Cochrane reviews | Searching for trials | Clinical Answers | About | Help

Cochrane Database of Systematic reviews | Review - Prognosis

Prognostic factors predicting an unprovoked seizure recurrence in children and adults following a first unprovoked seizure

Guleed Adan, Aidan Neligan, Sarah J Nevitt, Laura J Bonnett, Josemir W Sander, Anthony G Marson
Authors' declarations of interest

Version published: 10 October 2025 Version history
https://doi.org/10.1002/14651858.CD013848.pub2

Category	Key Findings / Details	Evidence Certainty
Strong Predictors (Higher Risk)	• **Abnormal EEG:** Associated with roughly **double the risk** of recurrence	**Moderate to Low**
Possible Predictors (Increased Risk)	• **Abnormal brain imaging** (CT or MRI) • **Nocturnal seizures** (occurring during sleep) • **Todd's paresis** (temporary post-seizure muscle weakness) • **Family history of epilepsy**	**Low**
Uncertain / Inconclusive Factors	• History of febrile seizures • Focal seizure onset or neurological deficits • Initial presentation as status epilepticus • Age (under 16) and male sex	**Very Low**
Main Conclusion	• An **abnormal EEG** is currently the most reliable single predictor. • Broader findings are limited by study inconsistencies and reporting gaps, highlighting the need for better standardized prospective studies.	—

Stigma and social restriction

EST 30th ANNIVERSARY ANNUAL MEETING

Pitfalls in Diagnosis

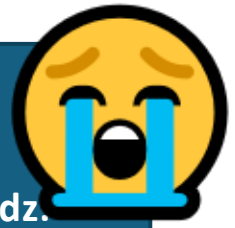
First Episode Seizure?

Seizure ?

Yes

Is it the real first SZ?

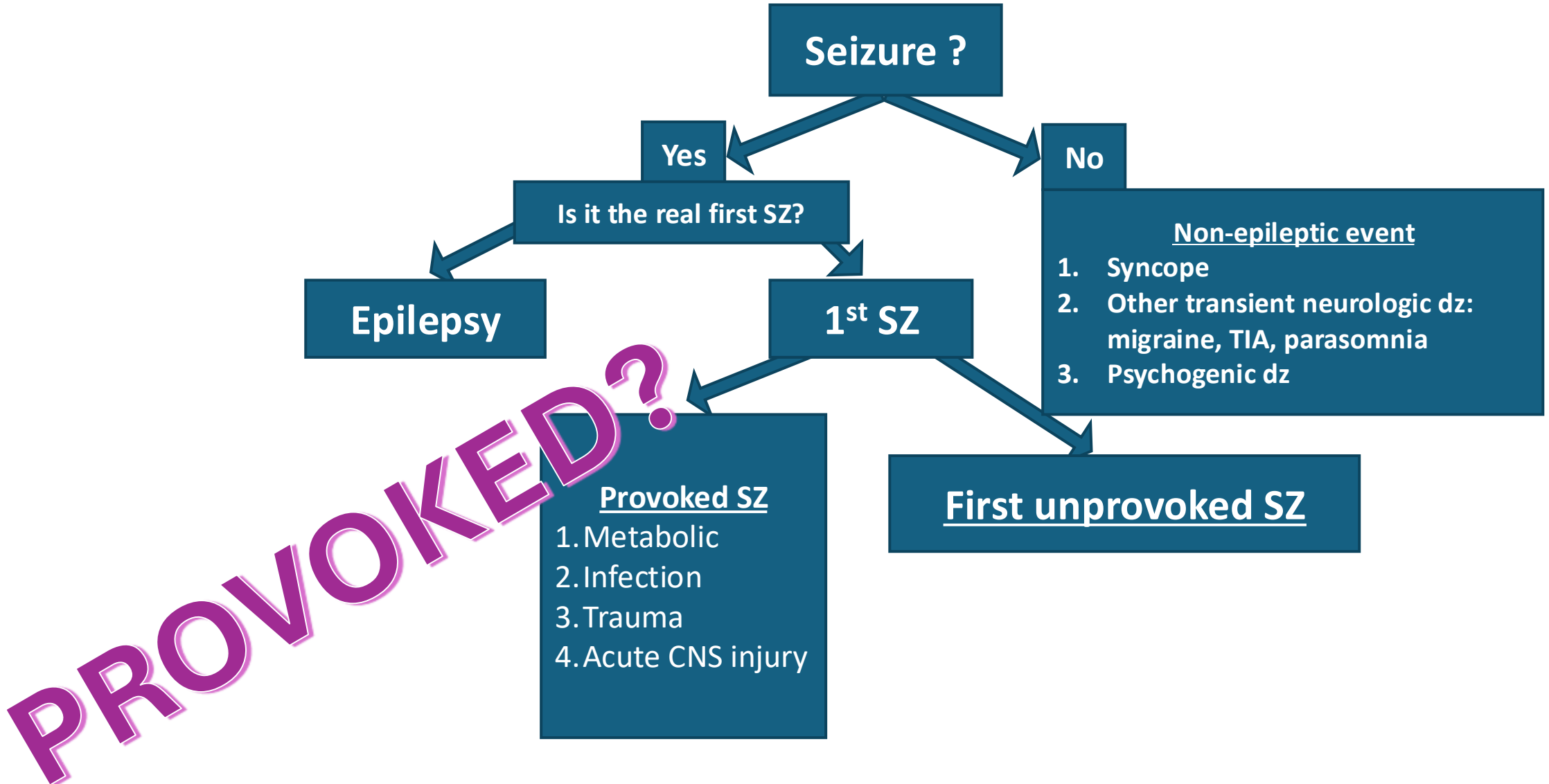
No



Non-epileptic event

1. Syncope
2. Other transient neurologic dz: migraine, TIA, parasomnia
3. Psychogenic dz

First Episode Seizure?



Recommendation for a definition of acute symptomatic seizure

*[1]Ettore Beghi, †Arturo Carpio, ‡Lars Forsgren, §Dale C. Hesdorffer, ¶Kristina Malmgren, #Josemir W. Sander, **Torbjorn Tomson, and §W. Allen Hauser

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)

SZs associated with febrile illness

- Minimum rectal temp 38.5°C (101.0°F)

Epilepsia, 51(4):671–675, 2010

TABLE 1-2

Categories of Toxins Causing Provoked Seizures

Category	Mechanism	Other clinical findings	Examples
Increased excitation			
Stimulants	Increased release of dopamine, serotonin, norepinephrine, and/or epinephrine or blocking their reuptake	Anxiety, delusions, delirium, diaphoresis, hypertension, tachycardia, hyperthermia, hyperreflexia, mydriasis, piloerection ECG monitoring should be considered for QRS and QTc prolongation and arrhythmias	Cocaine Amphetamines Phenethylamines Bath salts Serotonergic agents Bupropion Venlafaxine Synthetic cannabinoids Phencyclidine
Cholinergic agents	Binding of nicotinic or muscarinic receptors or inhibiting acetylcholinesterase	DUMBBELS (defecation, urination, miosis, bradycardia, bronchospasm, emesis, lacrimation, and salivation)	Organophosphates Nicotine Nerve gases (sarin and VX)
Glutamate agonists	Binding of *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), or kainate receptors	Somnolence, hallucinations, delirium, nausea and vomiting, diarrhea, salivation	Domoic acid (shellfish poisoning) *Amanita muscaria* mushroom ingestion

CONTINUUM (MINNEAP MINN) 2022;28(2, EPILEPSY):230–260.

Category	Mechanism	Other clinical findings	Examples
Increased excitation or withdrawal of central nervous system (CNS) depressants			
γ-Aminobutyric acid (GABA) antagonists	Blockage of GABA-ergic neurons or abrupt withdrawal of CNS depressants	Tremor, tachycardia, hypertension, diaphoresis, nausea, anxiety, irritability, insomnia, hallucinations	Tramadol Antibiotics: isoniazid (depletes pyridoxine, which inhibits GABA synthesis from glutamate), penicillin, cephalosporins, carbapenems, fluoroquinolones Abrupt withdrawal of GABA-ergic agents such as alcohol, benzodiazepines, baclofen, barbiturates Antidepressants and antipsychotics including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), phenothiazines
Decreased CNS inhibition			
Histamine antagonists	Antagonism at histamine receptors	Confusion, ataxia, hallucinations, delirium, dry mucous membranes, mydriasis	Histamine antagonists including diphenhydramine, doxylamine, hydroxyzine, chlorpheniramine
Adenosine antagonists	Antagonism of adenosine	Cardiac dysrhythmias	Theophylline, caffeine

ECG = electrocardiogram.

CONTINUUM (MINNEAP MINN) 2022;28(2, EPILEPSY):230–260.

Investigations: Pitfalls

- **Electroencephalography**
- **Neuroimaging**

Electroencephalography

- 18 – 56% of children and 12-50% of adults presenting with new-onset seizures have epileptiform abnormality found on routine EEG
- More diagnostic yield in early EEG and sleep deprivation EEG

- Pitfalls: 3% of people without epilepsy may show epileptiform discharges → False positive

CONTINUUM (MINNEAP MINN) 2022;28(2, EPILEPSY):230–260.

Electroencephalogram epileptiform abnormalities in candidates for aircrew training

R.P. Gregory, T. Oates and R.T.G. Merry

Princess Alexandra Hospital, Royal Air Force Wroughton, Swindon (UK)

(Accepted for publication: 11 September 1992)

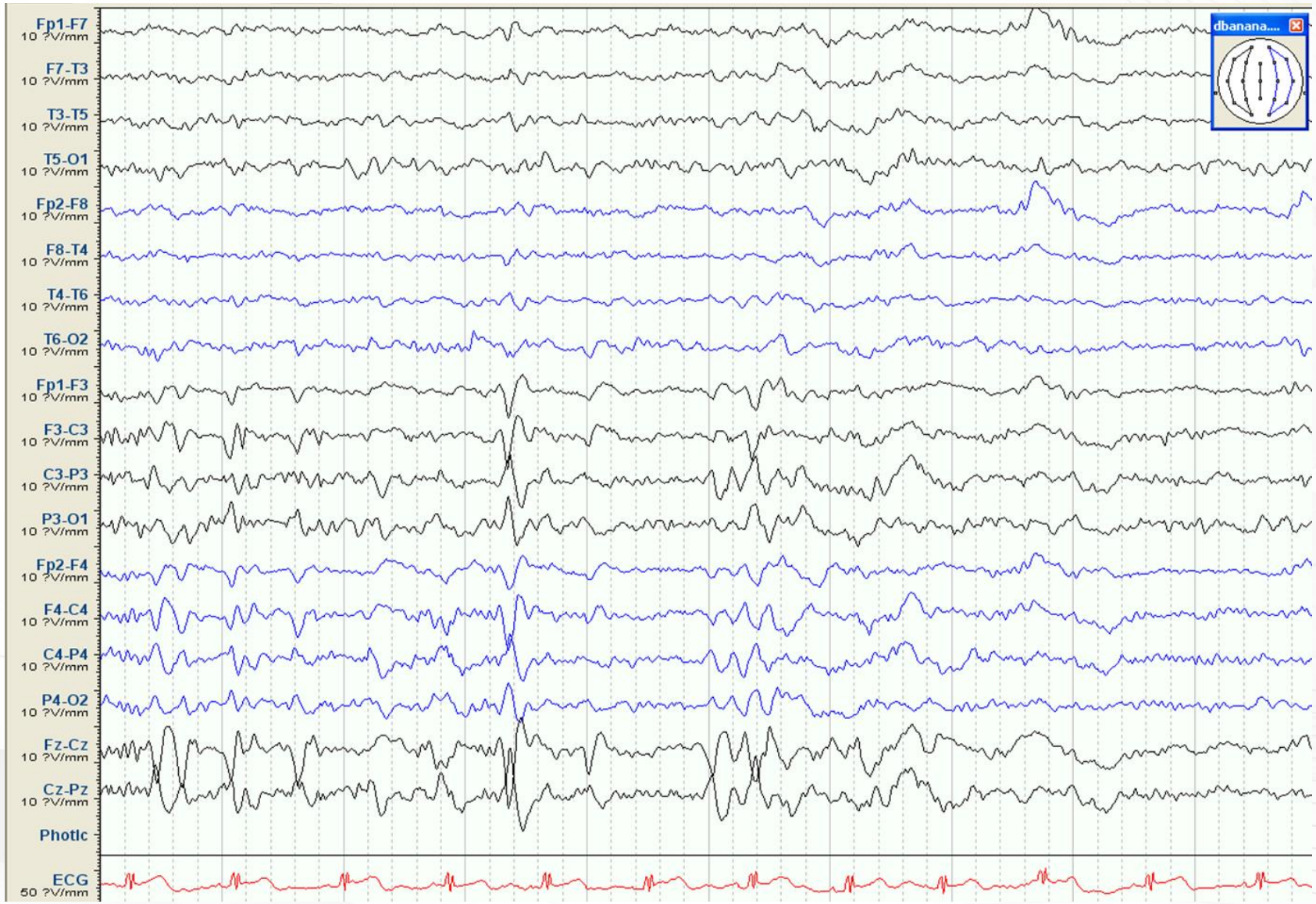
- 30 years the Royal Air Force has used the EEG as part of the medical screening of candidates for aircrew training.
- A total of 13,658 males aged 17-25 years.
- 0.5% of these showed unequivocal epileptiform discharges, 58% occurring only on photic stimulation.
- Exclude → 6 and 14 Hz positive spikes, 6 Hz spike and wave
- Chance of healthy individuals with EEG abnormalities epileptiform discharges is **2-3%.**

Electroencephalography and clinical Neurophysiology, 86 (1993) 75- 77

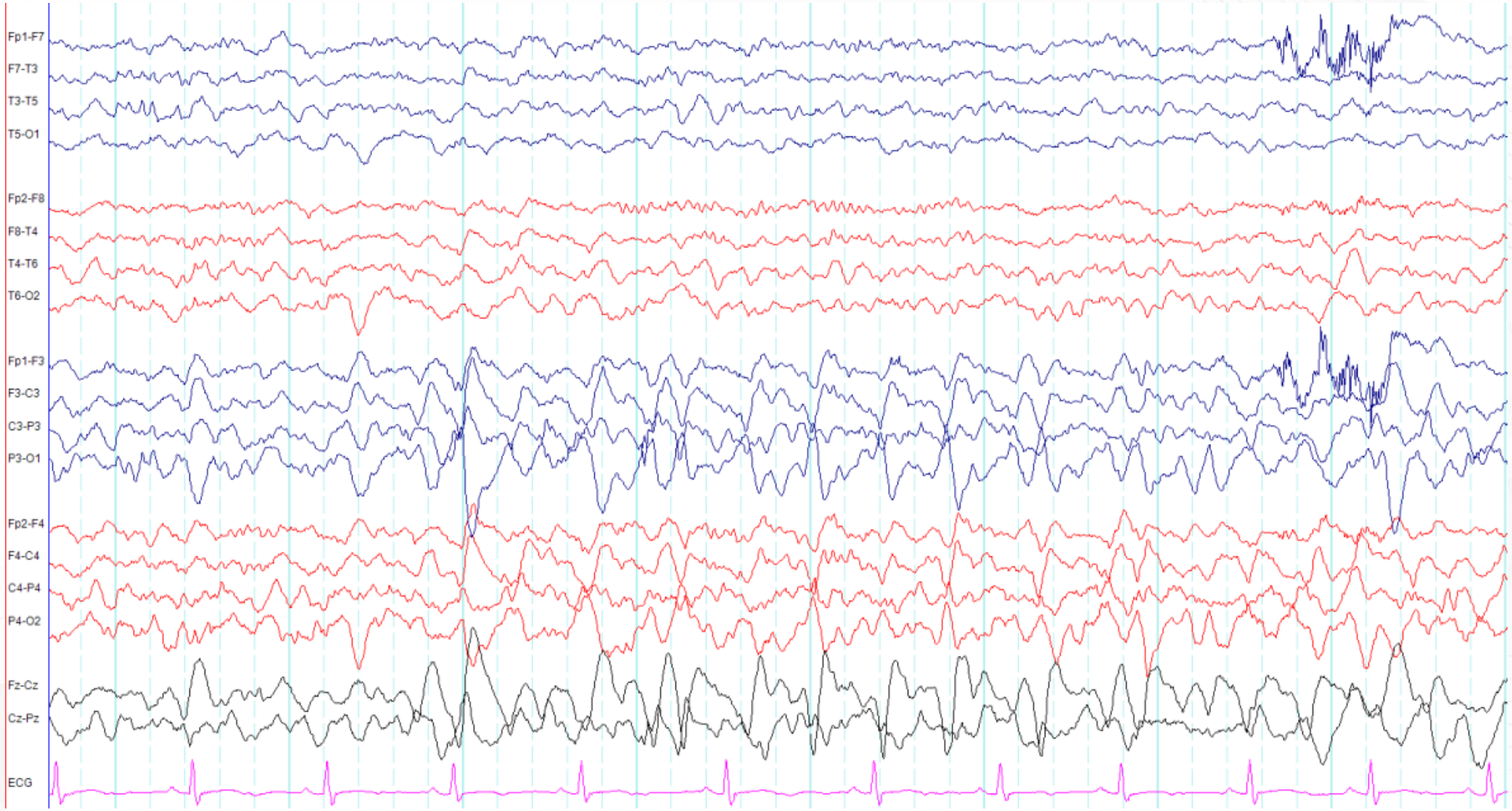
Caveats; normal/normal variants

- Children: vertex sharp waves, hypnagogic hypersynchrony
- Adolescents and adults: wicket waves and rhythmic temporal theta of drowsiness

Vertex sharp transients

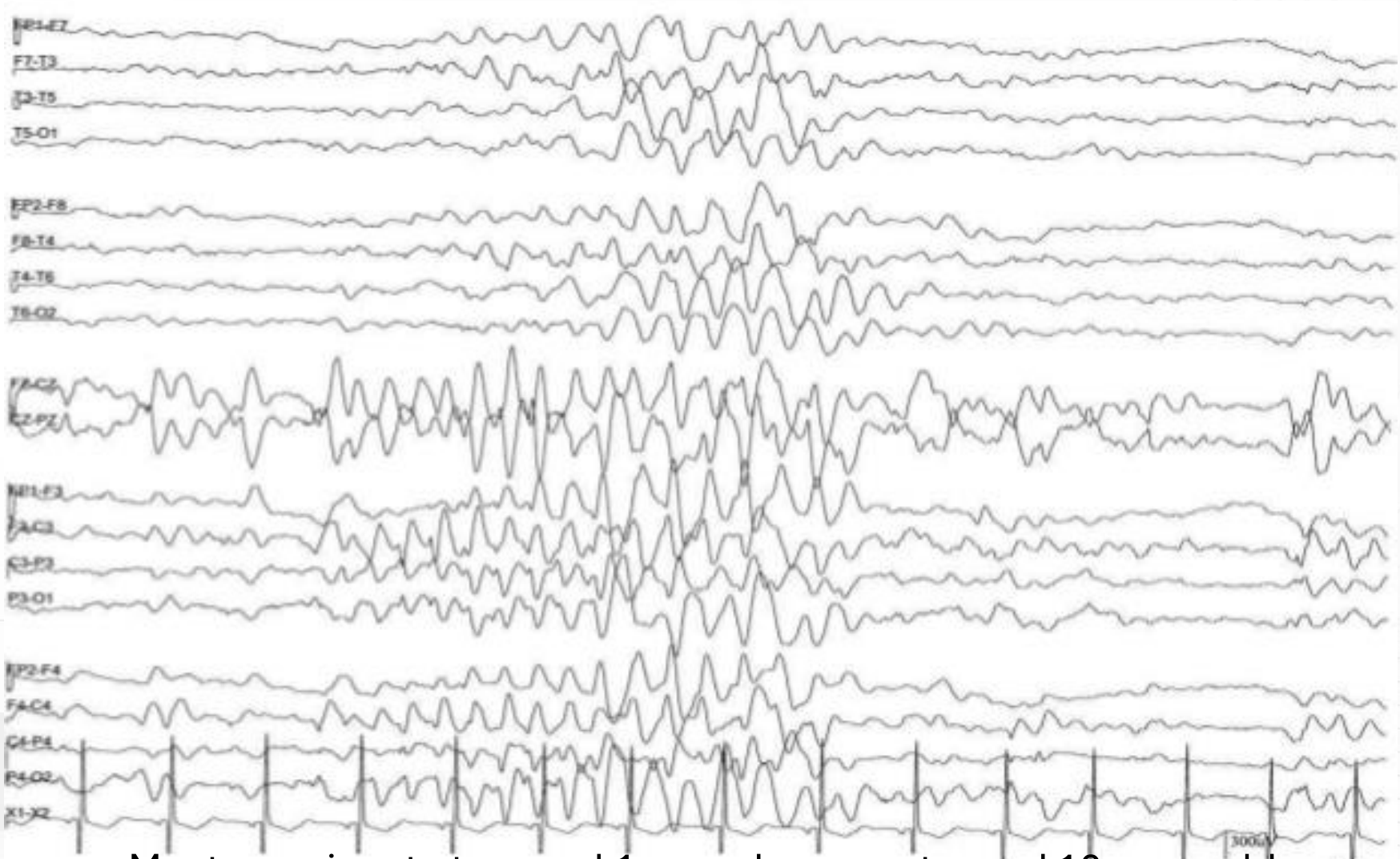


Vertex waves in runs



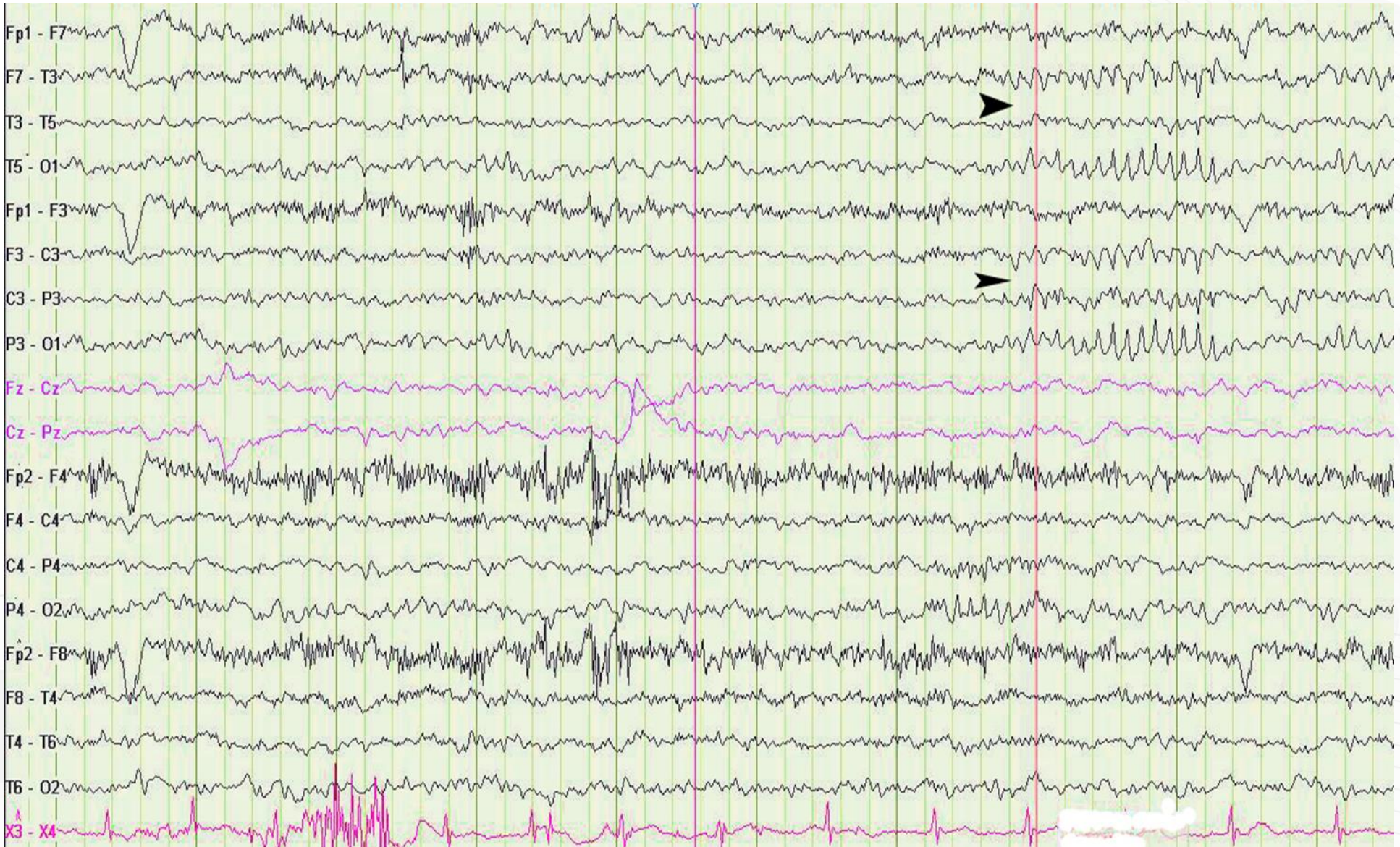
Hypnagogic hypersynchrony

Rhythmic bilateral synchronous high amplitude theta with widely distribution

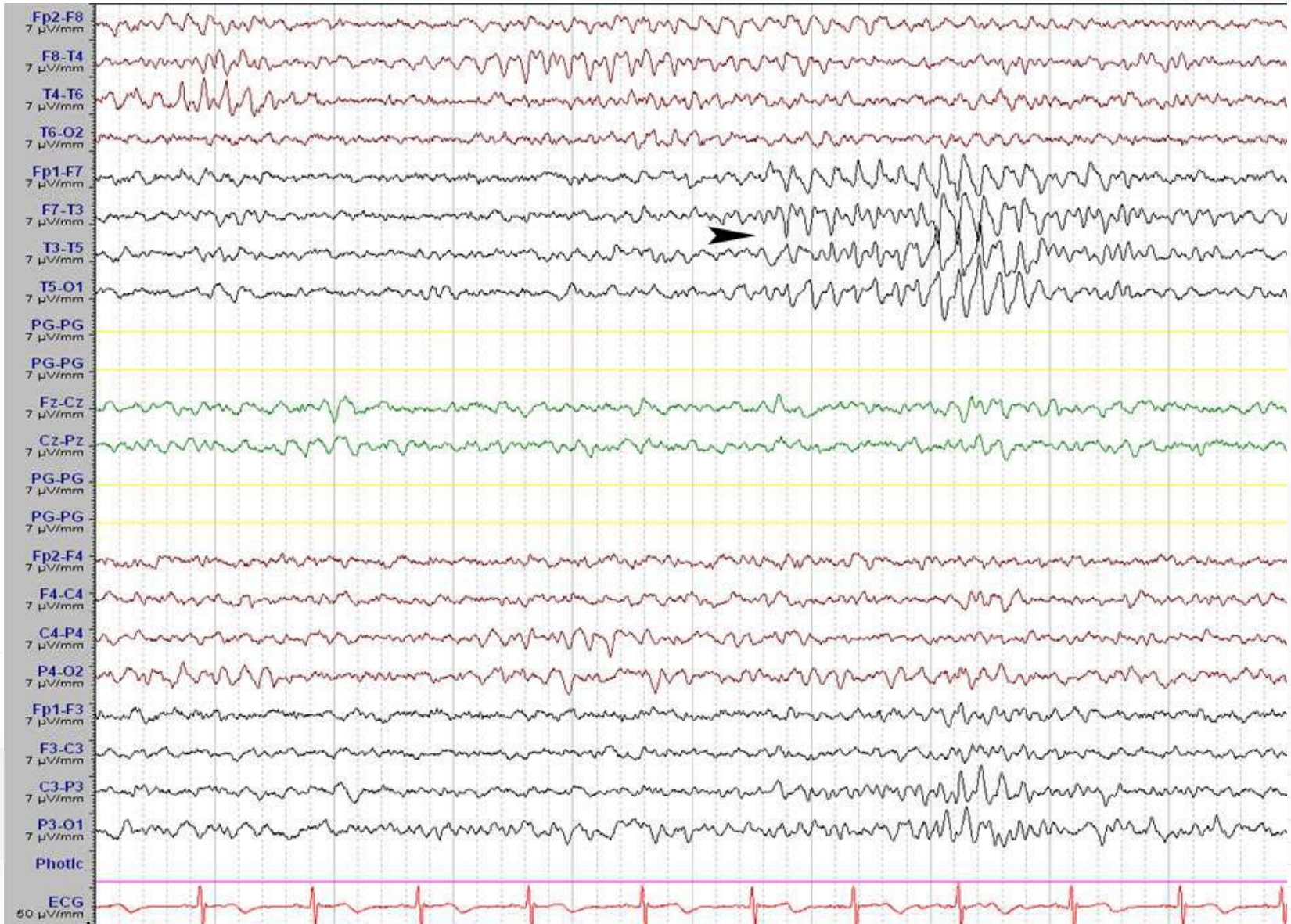


Most prominent at around 1 year, decrease toward 10 years old

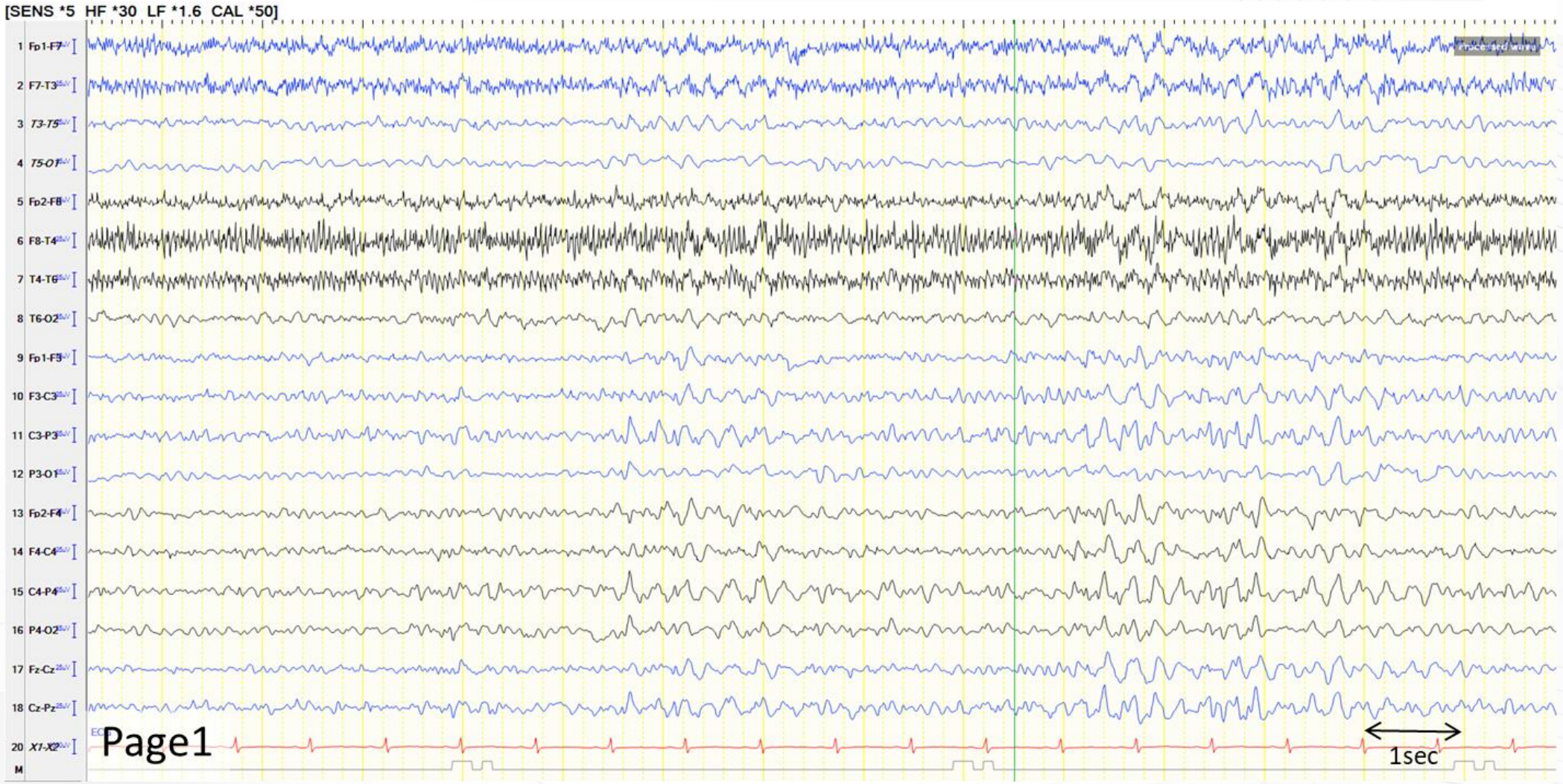
Wicket spikes

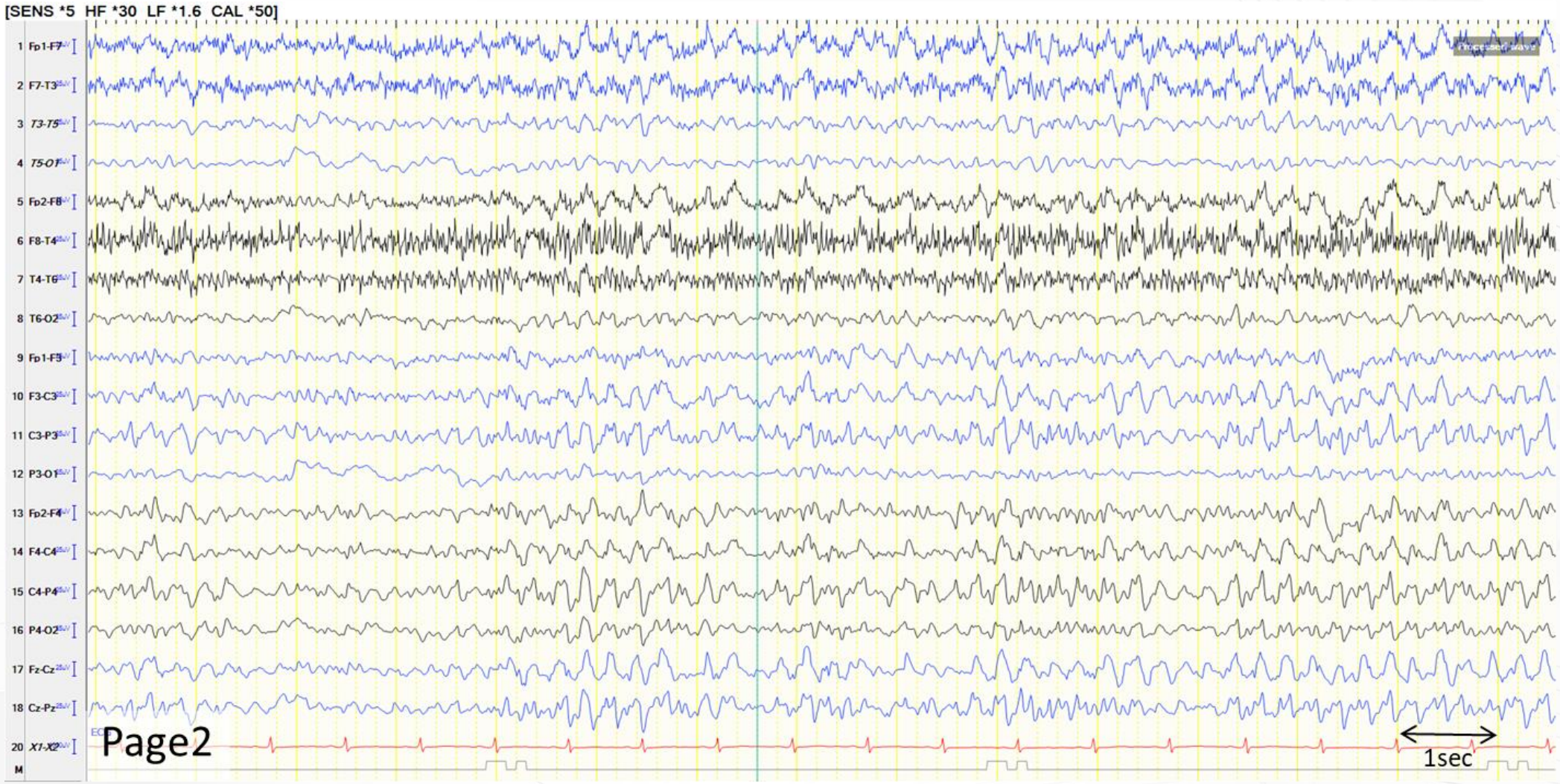


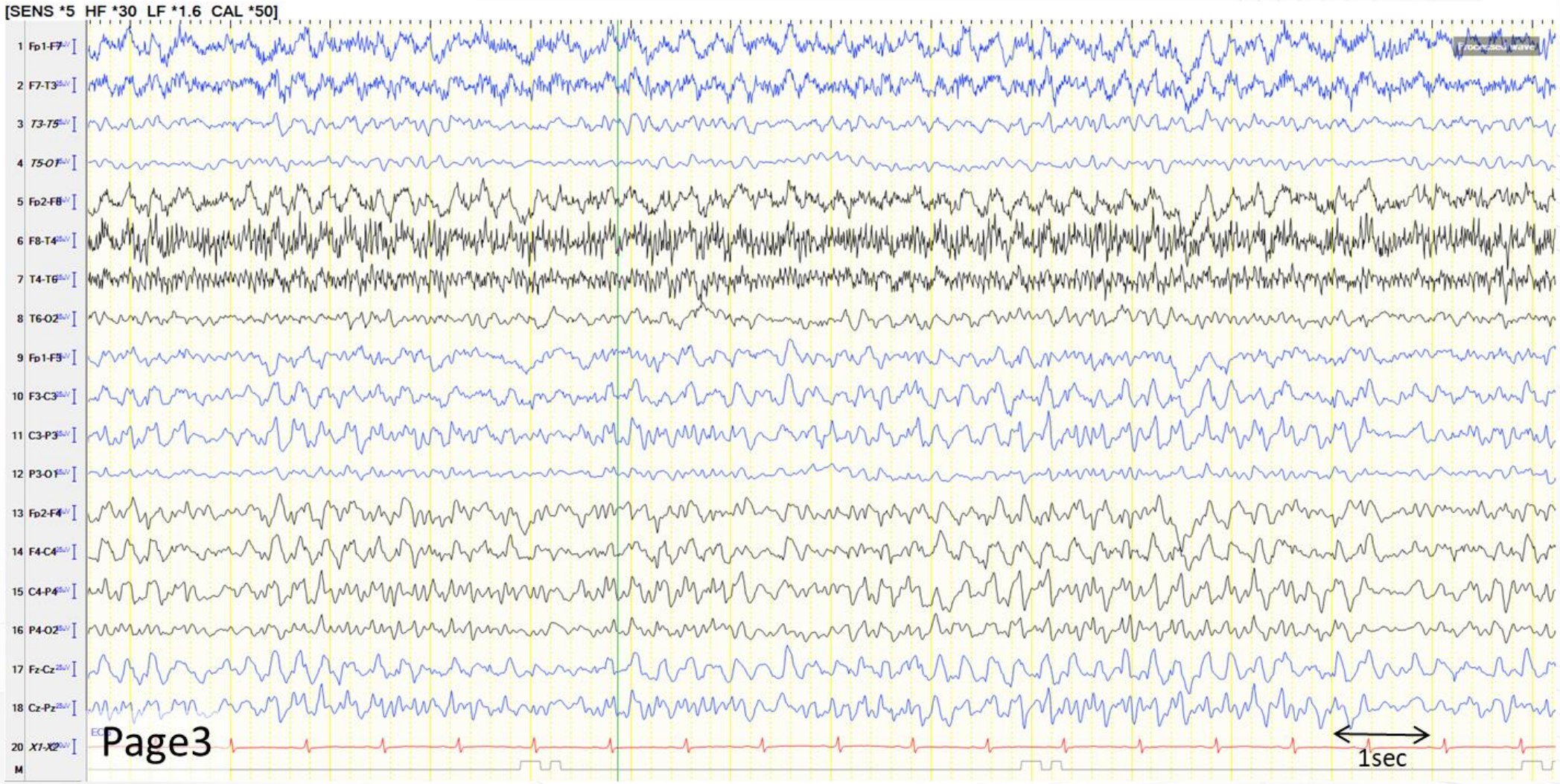
RMTD

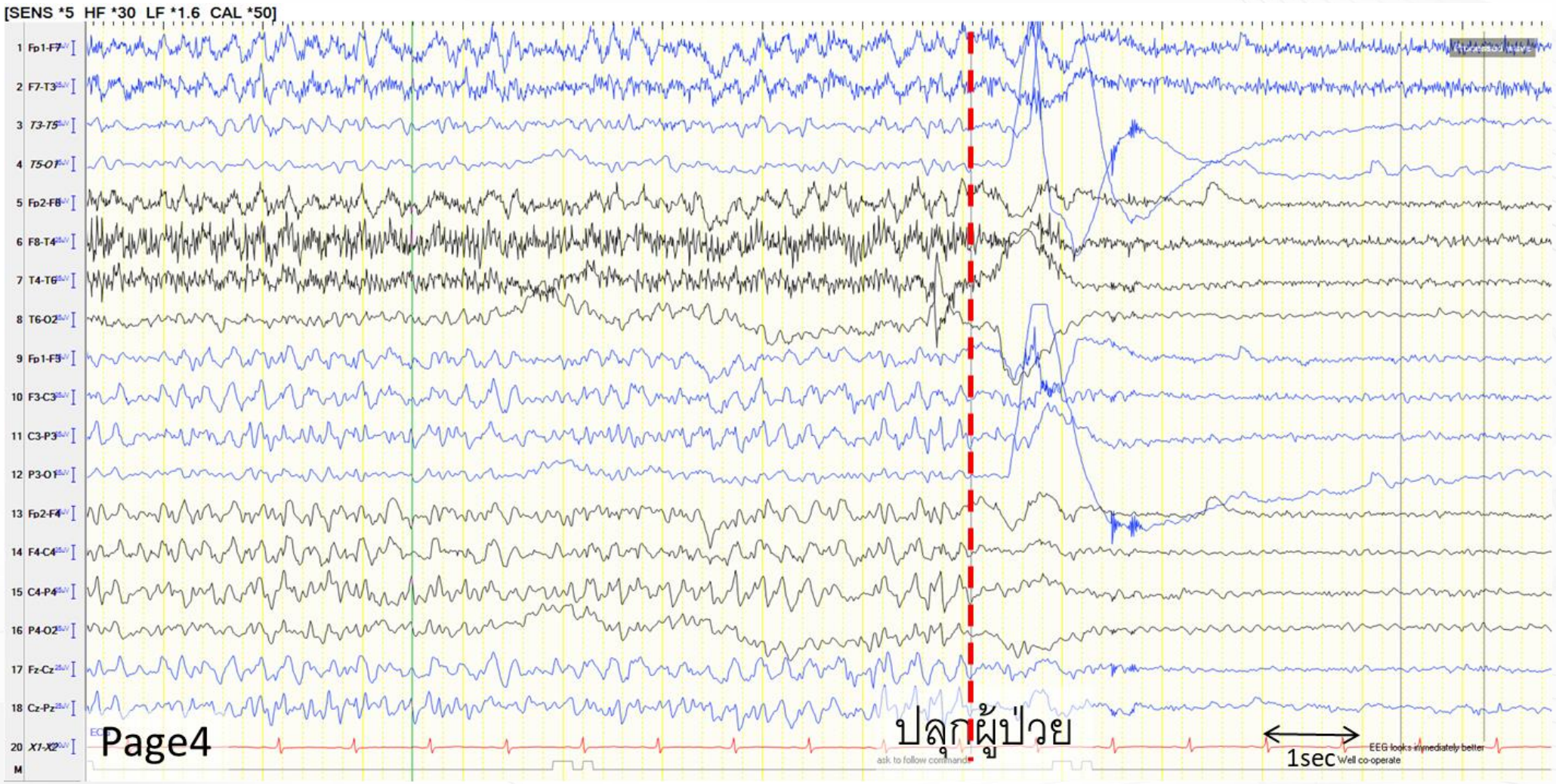

Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
PG-PG
PG-PG
Fz-Cz
Cz-Pz
PG-PG
PG-PG
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Photic
ECG
7 µV/mm
50 µV/mm

SREDA


[SENS *5 HF *30 LF *1.6 CAL *50]
1 Fp1-F7
2 F7-T3
3 T3-T5
4 T5-O1
5 Fp2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fp1-F3
10 F3-C3
11 C3-P3
12 P3-O1
13 Fp2-F4
14 F4-C4
15 C4-P4
16 P4-O2
17 Fz-Cz
18 Cz-Pz
20 X1-X2
M
Page1
1sec


[SENS *5 HF *30 LF *1.6 CAL *50]
1 Fp1-F7
2 F7-T3
3 T3-T5
4 T5-O1
5 Fp2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fp1-F3
10 F3-C3
11 C3-P3
12 P3-O1
13 Fp2-F4
14 F4-C4
15 C4-P4
16 P4-O2
17 Fz-Cz
18 Cz-Pz
20 X1-X2
M
Page2
1sec


[SENS *5 HF *30 LF *1.6 CAL *50]
1 Fp1-F7
2 F7-T3
3 T3-T5
4 T5-O1
5 Fp2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fp1-F3
10 F3-C3
11 C3-P3
12 P3-O1
13 Fp2-F4
14 F4-C4
15 C4-P4
16 P4-O2
17 Fz-Cz
18 Cz-Pz
20 X1-X2
M
Page3
1sec


[SENS *5 HF *30 LF *1.6 CAL *50]
1 Fp1-F7
2 F7-T3
3 T3-T5
4 T5-O1
5 Fp2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fp1-F3
10 F3-C3
11 C3-P3
12 P3-O1
13 Fp2-F4
14 F4-C4
15 C4-P4
16 P4-O2
17 Fz-Cz
18 Cz-Pz
20 X1-X2
M
Page4
ปลุกผู้ป่วย
1sec
EEG looks immediately better
Well co-operate
ask to follow command

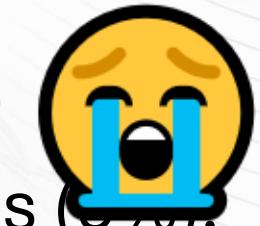
Neuroimaging

- MRI is preferable to CT (add on benefit 13%)
  - More sensitivity for: focal cortical dysplasia, mesial temporal sclerosis, low-grade gliomas, cavernous malformations, lesions at base of skull regions
- CT is more sensitive than MRI for calcified lesions or bone lesions

CONTINUUM (MINNEAP MINN) 2022;28(2, EPILEPSY):230–260.

MRI-identified pathology in adults with new-onset seizures

- potentially epileptogenic lesions were detected in 23%.
- **epileptic seizure (28%) vs nonepileptic event (8%) (p,0.001)**
- gliosis or encephalomalacia (49%), tumors (15%), cavernomas (6%), and mesial temporal sclerosis (9%)
- EEG normal in 55% of pts with epileptogenic lesions



Hakami T, et al. Neurology 2013;81:920–927

The "First Seizure" Dilemma – To Treat or Not to Treat

- Immediate ASM treatment delays 2nd SZ
- 14 pts to prevent 1 SZ in 1-2 year
- Long-term remission: no different
- AE and stigma need to be considered
- Investigation may have false positive

Clinical Decision making

Clinical Scenario	Estimated Recurrence Risk	Recommended Action
Normal EEG, Normal MRI, No prior insult	Low (~20–30% at 2 years)	**Defer treatment.** Counsel on lifestyle, driving restrictions, and seizure precautions.
Epileptiform EEG OR Structural lesion on MRI	High (>60% at 10 years)	**Initiate ASM monotherapy.** (Meets ILAE epilepsy criteria).
High-risk occupation / Driving necessity / Patient anxiety	Variable	**Shared decision-making.** Weigh ASM side effects vs. psychosocial/occupational consequences of a second event.