# Molecular Biomarkers of Alzheimer's Disease: Contribution to Understanding Pathogenesis and Improving Early Diagnosis

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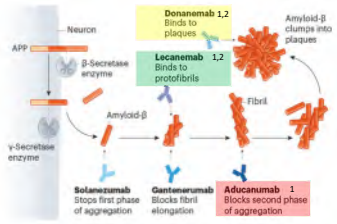
SERBIA

## Anti-amyloid monoclonal antibodies in the treatment of AD




1 - Approved by FDA 2- Approved by EMA

The indication for anti-amyloid therapy (AAT) is **mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease**.

**Eligibility criteria:**

1. **Biomarker-confirmed Alzheimer's pathology** is required prior to treatment initiation.

2. **ApoE genotyping** must be performed, and ApoE4 homozygotes are excluded due to high ARIA risk.

## Biomarkers in the diagnosis of AD

**Clinic of Neurology, University Clinical Center Niš**

**The aim** of the project was to introduce biomarkers into clinical practice and to establish quantitative diagnostic approaches to Alzheimer's disease, including neuroradiology, neuropsychology, and functional assessment (IADL).

**CSF AD biomarkers:**

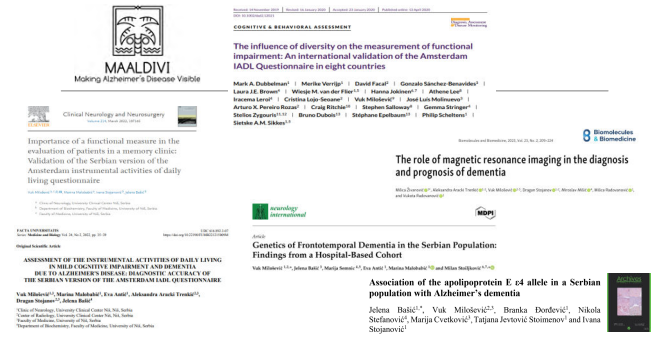
- **EUROIMMUN ELISA** since 2021 (Faculty of Medicine, University of Niš)
  - Measured **Aβ42**, **Aβ40**, **t-tau**, **p-tau**
  - Derived ratio **Aβ42/Aβ40**
- **Roche Elecsys ECLIA** since 2023 (Center for Medical Biochemistry, UKC Niš):
  - Measured **Aβ42**, **t-tau**, **p-tau**
  - Derived ratios **p-tau/Aβ42** and **t-tau/Aβ42**

MAALDIVI
Making Alzheimer's Disease Visible

Research Project No. 44/2020
Faculty of Medicine, University of Niš

**ApoE genotyping** (Laboratory for Medical genetics, Faculty of Medicine, University of Niš)

MRI volumetry, various plasma and CSF analytes, A-IADL-Q adaptation etc.




## What is Alzheimer's Disease?

While we are now approaching the era of disease-modifying therapy, it is surprising that the scientific debate about the nature and definition of Alzheimer's disease is still ongoing.

Alzheimer's Disease as biological entity

**Clifford R. Jack Jr.**
*Mayo Clinic*
*Rochester, MI, USA*

alzheimer's association

NIH National Institute on Aging

Alzheimer's Disease as clinical-biological entity

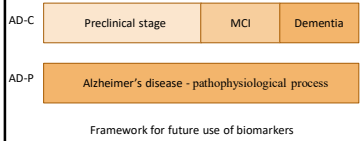
IWG International Working Group

**Bruno Dubois**
*ICM, Sorbonne Université*
*Paris, France*

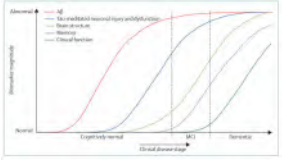
(Ossenkoppele i sar, 2022)

## Revised Criteria for the Diagnosis of AD

The National Institute on Aging / Alzheimer's Association diagnostic guidelines for Alzheimer's disease (NIA-AA) 2011.




Framework for future use of biomarkers



Dynamic biomarkers of the Alzheimer's pathological cascade

(Jack CR et al, 2011 ; Jack CR et al, 2011)

Funded by the European Union

Grant ID: 101159214

## Biological definition of AD (NIA-AA, 2018) – Research criteria

**A+ T+ = AD**, regardless of the clinical presentation

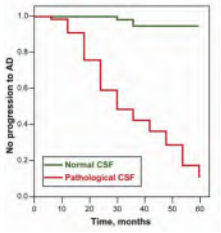
| | | | |
|---|---|---|---|
| **A** | ▪ Deposition of β-amyloid<br>▪ Amyloid plaques | ▪Amyloid PET<br>▪**$A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ in CSF** | |
| **T** | ▪ Aggregation of Tau protein<br>▪ Neurofibrillary tangles | ▪Tau PET<br>▪**P-tau in CSF** | |
| **(N)** | ▪ Neurodegeneration | ▪MRI<br>▪FDG-PET<br>▪***T-tau in CSF*** | |

NIA-AA, 2018 research criteria include three categories of biomarkers: A, T, N. Each biomarker category refers to distinct aspects of AD pathology

| Biomarker Profile | Cognitively Unimpaired | MCI | Dementia | |
|---|---|---|---|---|
| $A^-\ T^-\ (N)^-$ | Normal AD biomarkers, cognitively unimpaired | Normal AD biomarkers with MCI | Normal AD biomarkers with dementia | Normal |
| $A^+\ T^-\ (N)^-$ | Preclinical Alzheimer's pathologic change | Alzheimer's pathologic change with MCI | Alzheimer's pathologic change with dementia | Alzheimer's continuum |
| $A^+\ T^+\ (N)^-$ | Preclinical AD | AD with MCI | AD with dementia | |
| $A^+\ T^-\ (N)^+$ | Alzheimer's and concomitant suspected non-Alzheimer's pathologic change, cognitively unimpaired | Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with MCI | Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with dementia | |
| $A^-\ T^+\ (N)^-$ | Non-Alzheimer's pathologic change, cognitively unimpaired | Non-Alzheimer's pathologic change with MCI | Non-Alzheimer's pathologic change with dementia | Non-AD pathologic change |
| $A^-\ T^+\ (N)^+$ | Non-Alzheimer's pathologic change, cognitively unimpaired | Non-Alzheimer's pathologic change with MCI | Non-Alzheimer's pathologic change with dementia | |

Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Silverberg, N. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & dementia*, 14(4), 535-562.

## Conversion from MCI to dementia according to CSF AD biomarker status




The incidence of dementia among patients with MCI was:
**27% per year** in those with **positive CSF biomarkers**, and
**1% per year** in those with **negative CSF biomarkers**..

For the first time, AD biomarkers made it possible to predict which patients with MCI will convert to dementia, thereby successfully defining the predementia stage within Alzheimer's disease.

(Hansson i sar, 2006)

## Biomarker Positivity Weakly Predicts Clinical Conversion from Asymptomatic to Symptomatic AD

▪**Amyloid-positive but stable:**

▪INSIGHT study: 73/88 (83%) remained stable after 5 years (Dubois et al., 2018).

▪AIBL study: 111/137 (81%) stable after 6 years (Burnham et al., 2016).

▪Lifetime AD risk: 5–42% depending on age and sex (Brookmeyer & Abdalla, 2018).

▪**Amyloid + Tau positive:**

▪6/17 (35%) progressed to MCI or AD after 7 years (Hanseeuw et al., 2019).

▪5-year risk of progression 44% vs 11% (HR 2.79, 95% CI 1.14–6.9; p = 0.03) (Yu et al., 2019; Younes et al., 2019).

▪Tau PET: no or minimal acceleration in tracer uptake over 1–2 years (Jack et al., 2019).

THE LANCET Neurology

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

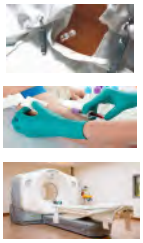
(Dubois et al, 2021)

## AA 2024 — Alzheimer's Disease Defined by β-Amyloid Pathology Biomarkers

**Core 1 + = AD**

alzheimer's association

| Biomarker category | CSF or plasma analytes | Imaging |
|---|---|---|
| **Core Biomarkers** | | |
| Core 1 | | |
| A ($A\beta$ proteinopathy) | $A\beta$ 42 | Amyloid PET |
| $T_1$: (phosphorylated and secreted AD tau) | p-tau217, p-tau181, p-tau231 | |
| Core 2 | | |
| $T_2$ (AD tau proteinopathy) | MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[2] | Tau PET |
| **Biomarkers of non-specific processes involved in AD pathophysiology** | | |
| N (injury, dysfunction, or degeneration of neuropil) | NfL | Anatomic MRI, FDG-PET |
| I (inflammation) Astrocytic activation | GFAP | |



Jack Jr, C. R., Andrews, J. S., Beach, T. G., Buracchio, T., Dunn, B., Graf, A., ... & Carrillo, M. C. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's & Dementia*, 20(8), 5143-5169.

## Biological staging of AD

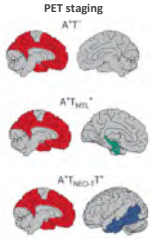
Conceptual biological staging with fluid biomarkers

Core 1 (A,T1)- diagnosis (Stage A)

T2- stages B,C,D

CSF and plasma

PET staging




(Jack CR et al, 2024)

## Relationship between biological and clinical stages

| Clinical Stage | Designation (NIA–AA 2024) |
|---|---|
| 0 | deterministic gene, asymptomatic, biomarkers negative |
| 1* | Asymptomatic, biomarker evidence only |
| 2 | Transitional decline |
| 3 | Cognitive impairment with early functional impact |
| 4 | Dementia with mild functional impairment |
| 5 | Dementia with moderate functional impairment |
| 6 | Dementia with severe functional impairment |

* "Although symptoms may not appear for years, the disease nonetheless exists at this initially detectable stage and will eventually produce symptoms if the individual lives long enough."

| | Stage 0 | clinical Stage 1 | clinical Stage 2 | clinical Stage 3 | clinical Stages 4-6 |
|---|---|---|---|---|---|
| Initial biological stage (A) | X | 1A | 2A | 3A | ~~4-6A~~ |
| Early biological stage (B) | X | 1B | 2B | 3B | ~~4-6B~~ |
| Intermediate biological stage (C) | X | 1C | 2C | 3C | ~~4-6C~~ |
| Advanced biological stage (D) | X | 1D | 2D | 3D | ~~4-6D~~ |

Copathology / Vulnerability

Cognitive Reserve / Resilience

(Jack CR et al, 2024)

## Plasma biomarkers of AD

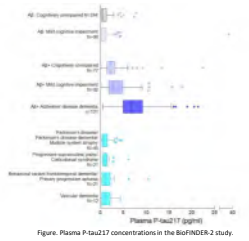


Figure. Plasma P-tau217 concentrations in the BioFINDER-2 study.

Plasma p-tau217 concentrations are elevated by 300–700% in patients with symptomatic Alzheimer's disease.

Fujirebio's Lumipulse G pTau217/Aβ42 Plasma Ratio is the first plasma biomarker for Alzheimer's disease approved by the FDA (PPV= 91.7%, NPV= 97.9%)

Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, Su Y, Chen Y, Serrano GE, Leuzy A, Mattsson-Carlgren N, Strandberg O, Smith R, Villegas A, Sepulveda-Falla D, Chai X, Proctor NK, Beach TG, Blennow K, Dage JL, Reiman EM, Hansson O. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2020 Aug 25;324(8):772-781.

| Aspect | AA 2024 (Biological) | IWG 2024 (Clinical-biological) |
|---|---|---|
| Definition of Alzheimer disease | "AD should be **defined biologically**, not based on a clinical syndrome." | "AD is a **clinical-biological construct**." |
| Implications for diagnosis in clinical setting | Presence of any abnormal Core 1 AD biomarker (Aβ42/40, pTau, etc.) is sufficient.<br><br>A biomarker-positive cognitively normal person **can be diagnosed with AD.** | Presence of objective cognitive deficits and AD biomarkers is needed.<br><br>A biomarker-positive cognitively normal person **cannot be diagnosed with AD***. |
| Implications in diagnostic disclosure | **Cognitively normal** persons with one positive core AD biomarker can be told they **have AD.** | **Cognitively normal** persons with positive AD biomarker can be told they are **at-risk for AD.** |
| Implications for phase 3 preventive clinical trials | **Biomarkers could be primary endpoints** in clinical trials.<br><br>Demonstration of efficacy on clinical parameters may not be necessary. | **Biomarkers cannot be primary endpoints** in clinical trials.<br><br>Demonstration of efficacy on clinical parameters is necessary. |

## Proposed Diagnostic Categories in the IWG 2024 Framework

**1. At-risk for AD**
Abnormal amyloid and/or tau biomarkers, but no cognitive or behavioral symptoms.
Represents a *risk state*, not the disease itself.

**2. Preclinical AD (genetic form)**
Asymptomatic carriers of pathogenic AD mutations who are biomarker-positive.

**3. Prodromal AD**
Mild cognitive impairment (MCI) with positive AD biomarkers (the early symptomatic stage).

**4. Alzheimer's Dementia**
Dementia syndrome with confirmed amyloid and tau pathology, including both typical and atypical variants.

**5. Mixed or Uncertain Presentations**
Cases with coexisting pathologies (e.g., vascular, Lewy body) or incomplete biomarker profiles.

(Dubois et al, 2024)

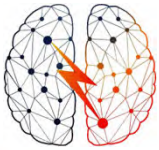
## Summary

- Biomarkers are essential for the early diagnosis of Alzheimer's disease and serve as the key inclusion criterion for anti-amyloid monoclonal antibody therapy.
- The biological definition of Alzheimer's disease identifies the disorder independently of clinical presentation, recognizing it even in asymptomatic individuals.
- The status of preclinical Alzheimer's disease remains a major point of disagreement between the AA and IWG frameworks.
- The upcoming implementation of plasma biomarkers in clinical practice will increasingly identify Stage 1 individuals, posing new diagnostic and management challenges for clinicians.

Summer School: Neurology and AI fusion

Sokobanja, 2026

Funded by the European Union
Grant ID 101159214




# Epilepsy

**-for PhD students in computer science-**

Stevo Lukić

MAY 28

## MAIN GOALS

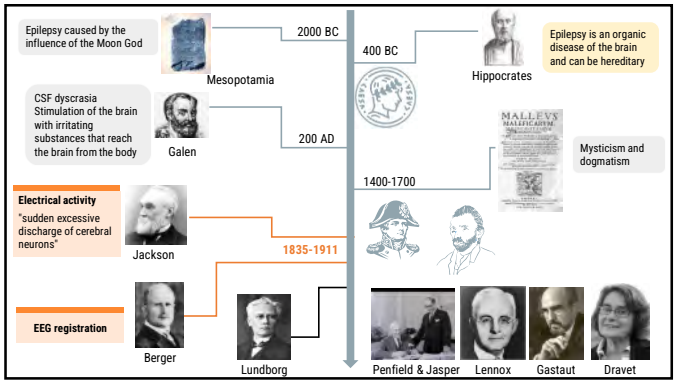
- Epilepsy is clinical, longitudinal, and multimodal
- Epilepsy is not merely an EEG classification problem
- Show how semiology, witness history, EEG, MRI, medication response, and longitudinal course are integrated
- Identify where general AI can help with signal, video, and wearable data
- Identify where LLMs can help with narratives, diaries, reports, and longitudinal summaries

## What clinicians want engineers to learn?

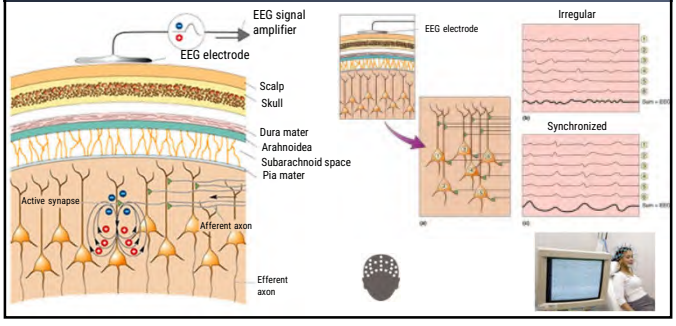
### Seizures are clinical events

- An epileptic seizure is a transient event caused by abnormal excessive or synchronous neuronal activity
- Epilepsy implies an enduring predisposition to unprovoked seizures, not just one event or one abnormal test
- Many conditions mimic epilepsy: syncope, psychogenic non-epileptic seizures, sleep events, migraine aura, movement disorders
- The witness narrative and video may be as important as the EEG signal

## DEFINITIONS AND PATHOPHYSIOLOGY




## Registration of electrical activity of the brain



Funded by the European Union
Grant ID: 101159214

## DEFINITIONS

Seizure ≠ Epilepsy

ILAE International League Against Epilepsy

**SEIZURE** 5-10%

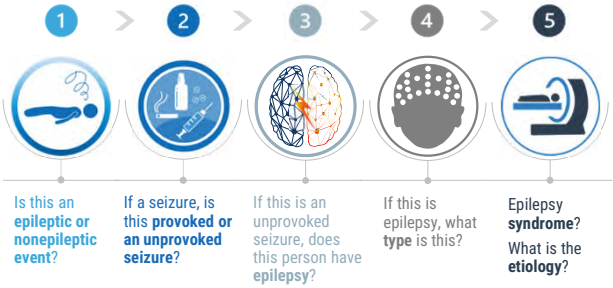
**Transient** appearance of signs or symptoms due to abnormal, excessive or synchronized neuronal activity in the brain

**EPILEPSY** 0.5-1%

A brain disease characterized by a **permanent predisposition** to generate epileptic seizures and with neurobiological, cognitive, psychological and social consequences of this condition

Fisher et al. (2005; 2014; 2017)

## Diagnostic procedure (questions)

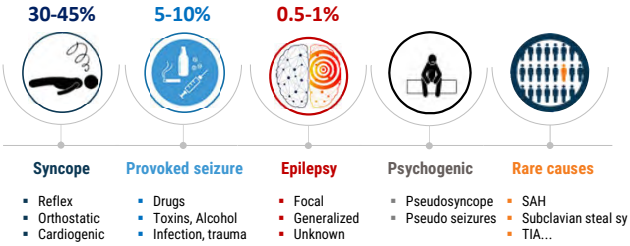



1

## Is this an epileptic or a nonepileptic event?

## The most common causes of TLOC

Cumulative lifetime prevalence (up to 70 years)




## SYNCOPE

Consequence of short-term **global** cerebral hypoperfusion

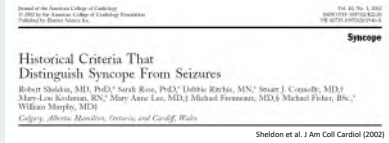
- A sudden interruption of cerebral flow for 6-8 s can be enough to cause a complete LOC
- ↓ systolic TA to ≤ 60 mm Hg → associated with syncope

| ≈ 60% | ≈ 25% | ≈ 15% |
|---|---|---|
| **REFLEX** | **ORTHOSTATIC** (Autonomic failure) | **CARDIOGENIC** (Cardiovascular) |
| ▪ Vasovagal<br>▪ Situational<br>▪ Carotid sinus syncope | ▪ Primary autonomic failure<br>▪ Secondary autonomic failure<br>▪ Drug-induced OH<br>▪ Loos of volume | ▪ Primary cardiac arrhythmias<br>▪ Bradycardia<br>▪ Tachycardia<br>▪ Drug-induced arrhythmias<br>▪ Structural diseases |

## SYNCOPE OR SEIZURE?

The most important diagnostic method: *History*

- **Fenomeni pred gubitak svesti**
  - Phenomena before loss of consciousness
  - Prodromal symptoms and signs
  - Position and circumstances in which loss of consciousness occurs
- **Phenomena during loss of consciousness**
  - Duration time
  - Muscle tone, time of occurrence of motor phenomena
- **Phenomena upon regaining consciousness**
  - Speed of recovery of consciousness
  - Duration of confusion


Syncope

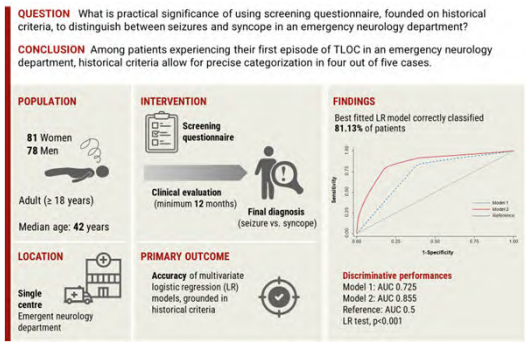
Historical Criteria That Distinguish Syncope From Seizures

Sheldon et al. J Am Coll Cardiol (2002)

9 Questions regarding the clinical characteristics of the event

Sn 94%, Sp 94%

Our expirience Sn 81.3%

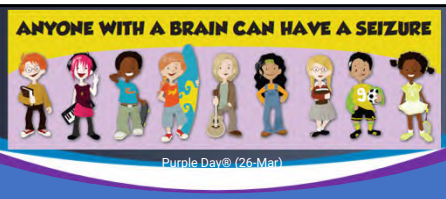


Lukić S, Stojanov A. Australas Emerg Care. 2024;27(2):142-147

## Seizure semiology: the clinical signal

What happened during the event?

- Onset: aura, sensory symptoms, fear, déjà vu, rising epigastric sensation, visual symptoms
- Awareness: retained, impaired, lost, uncertain.
- Motor features: automatisms, tonic posturing, clonic jerking, head/eye deviation, bilateral tonic-clonic activity
- Autonomic and postictal features: cyanosis, injury, confusion, fatigue, headache
- Duration, triggers, recovery, witness description, and video evidence are essential




2 If a seizure, is this provoked or an unprovoked seizure?

## SEIZURES

It can be provoked in any person if the strength of the provocation is sufficient!!

**Seizure**

Transient appearance of signs or symptoms due to abnormal, excessive or synchronized neuronal activity in the brain

**Provoked seizure**

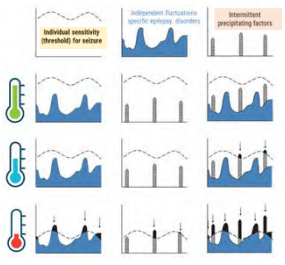
Seizures occurring at the time of a systemic insult or in close temporal association with a documented cerebral insult

**Unprovoked seizure**

An attack or a cluster of attacks within 24 h in a person older than 1 month in the absence of precipitating factors

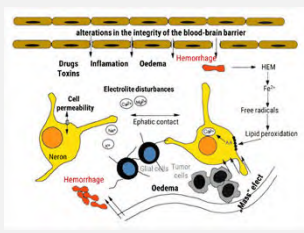
## Provoked seizures

Interactions of the fluctuating **threshold** for seizures determined by nonspecific **predisposing factors**



Engel (2014)

Pathophysiology of acute symptomatic seizures



Vaughan & Delanty (2002)

## Provoked seizures

≠ NOT EPILEPSY!!!

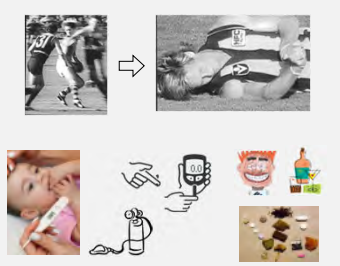
**An acute symptomatic lesion affecting an otherwise HEALTHY BRAIN**

**Acute brain damage (within 7 days)**

- Stroke
- Meningitis
- Abscess
- Trauma…

**Temporary effects of systemic, metabolic, toxic and other harmful factors**

- High fever
- Hypoglycemia
- Hypoxia
- Alcohol
- Cocaine
- Sleep deprivation…



3

**If this is an unprovoked seizure, does this person have epilepsy?**

## Epilepsy

### Practical definition

ILAE International League Against Epilepsy

**At least 2 unprovoked (or reflex) epileptic seizures**
Separate by time interval of more than 24 hours

- 1 unprovoked (or reflex) epileptic seizure +
- Probability of further attacks as in the case of 2 unprovoked attacks
  (General risk of recurrence ≥ 60% for 10 years)

**Diagnosis of epileptic syndrome**

Fischer RS et al. Epilepsia 2014; 55; 475-482

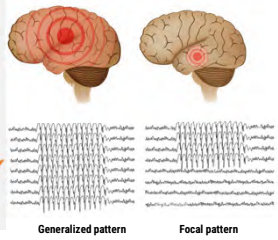
4

**If this is epilepsy, what type is this?**

## CLASSIFICATION OF EPILEPTIC SEIZURES

### Combination of clinical and EEG findings

- The clinical manifestations of seizures depend on the part of the brain where the epileptic discharge occurs
- A short-term disturbances of
  - Consciousness
  - Behaviors
  - Emotion
  - Motor functions
  - Sensory functions...
- EEG pattern
  - Generalized
  - Focal
  - Unknown



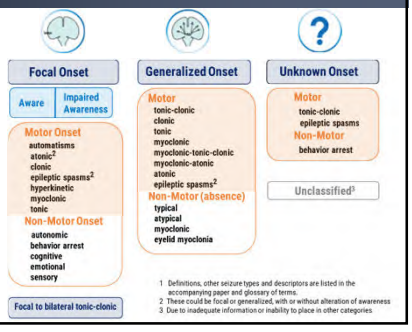
Generalized pattern | Focal pattern

**Initial symptoms/signs**

- the most useful features for identifying the regional brain network in which the seizure occurs
- For each type of attack, the start is consistent from one attack to the next
- Propagation patterns may involve the ipsilateral and/or contralateral hemisphere
- They may allow the identification of a discrete brain area, lobe, or hemisphere involved in the initiation and propagation of seizures

## CLASSIFICATION OF EPILEPTIC SEIZURES (2017)

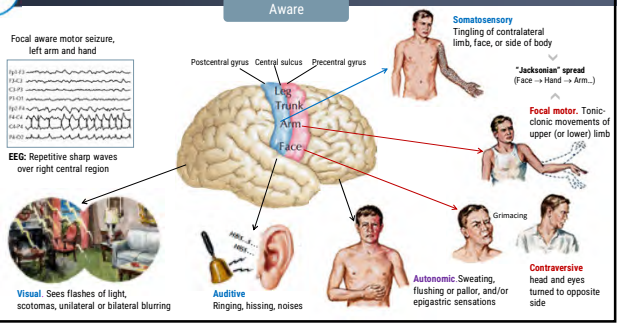
1. **Focal vs. generalized**
2. **Awareness during an attack**
   Defined in relation to whether the patient is fully aware of himself and his surroundings during the attack, even if he is immobile
3. **Motor vs. non-motor onset**

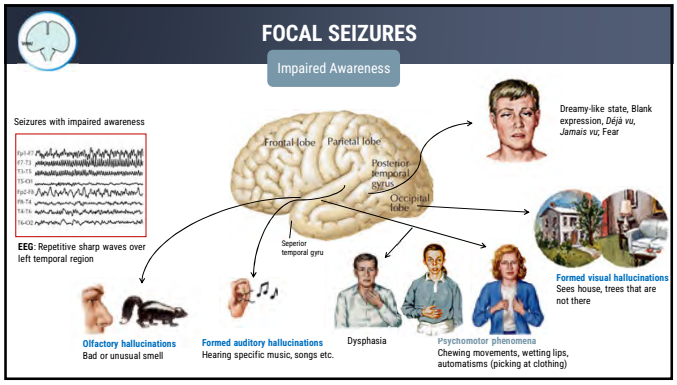


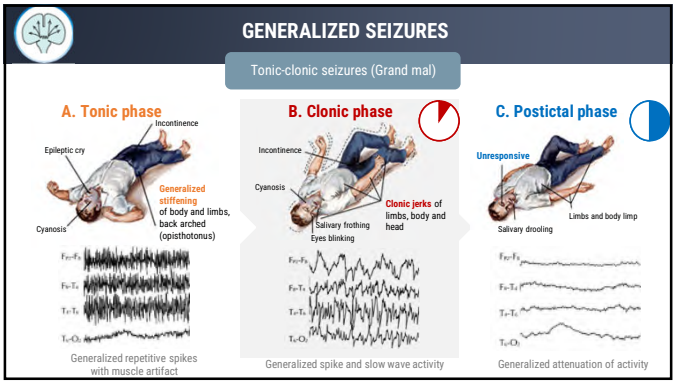

Fisher et al. 2017

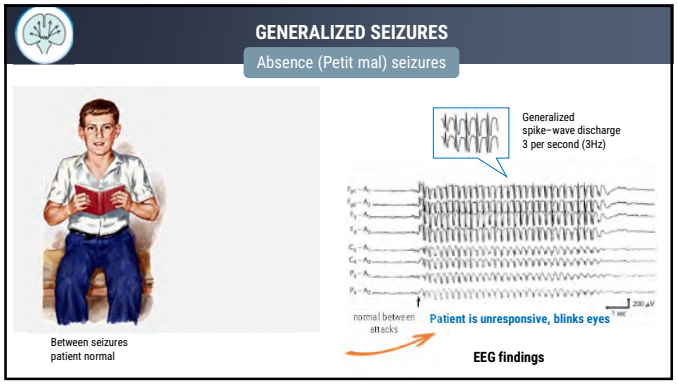
## Focal seizures

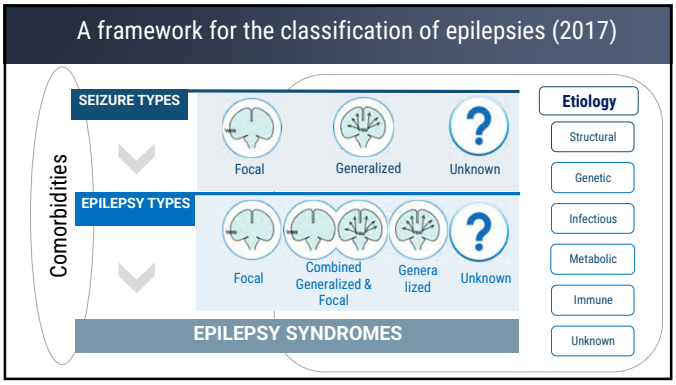
Aware



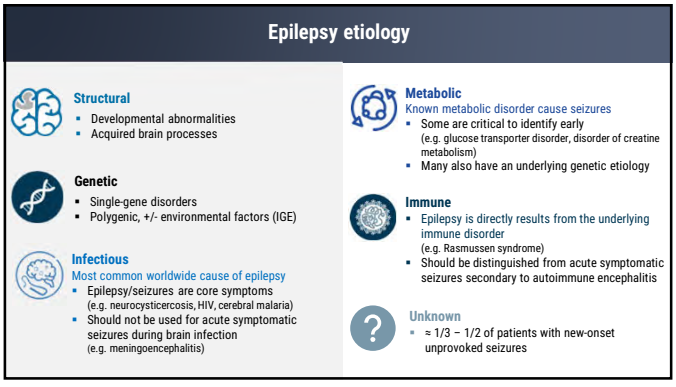

FOCAL SEIZURES
Impaired Awareness
Seizures with impaired awareness
EEG: Repetitive sharp waves over left temporal region
Frontal lobe
Parietal lobe
Posterior temporal gyrus
Occipital lobe
Superior temporal gyru
Dreamy-like state, Blank expression, Déjà vu, Jamais vu; Fear
Formed visual hallucinations
Sees house, trees that are not there
Olfactory hallucinations
Bad or unusual smell
Formed auditory hallucinations
Hearing specific music, songs etc.
Dysphasia
Psychomotor phenomena
Chewing movements, wetting lips, automatisms (picking at clothing)


GENERALIZED SEIZURES
Tonic-clonic seizures (Grand mal)
A. Tonic phase
Incontinence
Epileptic cry
Generalized stiffening of body and limbs, back arched (opisthotonus)
Cyanosis
Generalized repetitive spikes with muscle artifact
B. Clonic phase
Incontinence
Cyanosis
Clonic jerks of limbs, body and head
Salivary frothing
Eyes blinking
Generalized spike and slow wave activity
C. Postictal phase
Unresponsive
Limbs and body limp
Salivary drooling
Generalized attenuation of activity


GENERALIZED SEIZURES
Absence (Petit mal) seizures
Between seizures patient normal
Generalized spike–wave discharge 3 per second (3Hz)
normal between attacks
Patient is unresponsive, blinks eyes
EEG findings


A framework for the classification of epilepsies (2017)
Comorbidities
SEIZURE TYPES
Focal
Generalized
Unknown
EPILEPSY TYPES
Focal
Combined Generalized & Focal
Genera lized
Unknown
EPILEPSY SYNDROMES
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown


ETIOLOGY


Epilepsy etiology
Structural
Developmental abnormalities
Acquired brain processes
Genetic
Single-gene disorders
Polygenic, +/- environmental factors (IGE)
Infectious
Most common worldwide cause of epilepsy
Epilepsy/seizures are core symptoms (e.g. neurocysticercosis, HIV, cerebral malaria)
Should not be used for acute symptomatic seizures during brain infection (e.g. meningoencephalitis)
Metabolic
Known metabolic disorder cause seizures
Some are critical to identify early (e.g. glucose transporter disorder, disorder of creatine metabolism)
Many also have an underlying genetic etiology
Immune
Epilepsy is directly results from the underlying immune disorder (e.g. Rasmussen syndrome)
Should be distinguished from acute symptomatic seizures secondary to autoimmune encephalitis
Unknown
≈ 1/3 – 1/2 of patients with new-onset unprovoked seizures

## DIAGNOSTIC PROCEDURES

## Diagnostic tests

A normal NMR or EEG does not rule out dg. epilepsy!!

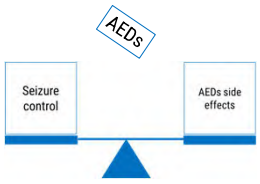
| Laboratory analyzes (blood, urine) | Toxicological analyses | Neuroimaging | CSF analysis | EEG |
|---|---|---|---|---|
| Metabolic causes of seizures, liver or kidney disease... | Detection of toxins in risk groups | Detection of structural brain damage, diagnosis of the causes of symptomatic epilepsies | Meningitis, encephalitis, HIV infection | Supporting the diagnosis of epilepsy Determining the type of seizures and syndrome |

## THERAPY

## EPILEPSY THERAPY

- Treatment of the underlying disease
- Avoidance of precipitating factors
- Pharmacotherapy
- Surgical therapy
- Alternative methods of treatment
  - Vagus nerve stimulation
  - Ketogenic diet
  - Other

- Basic goals
  - Seizure control
  - No (minimal) side effects




## AVOIDANCE OF PRECIPITATING FACTORS

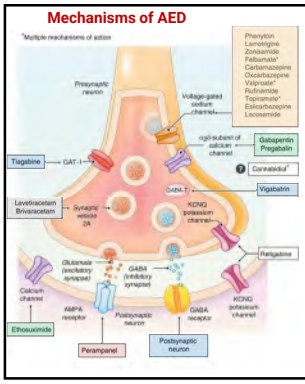
**Universal precipitating factors**

- Sleep deprivation
- Stress
- Alcohol, caffeine, drugs…
- Fever

**Specific stimuli (in reflex epilepsy)**

- Flickering light
- Specific music, reading …


## Mechanisms of AED

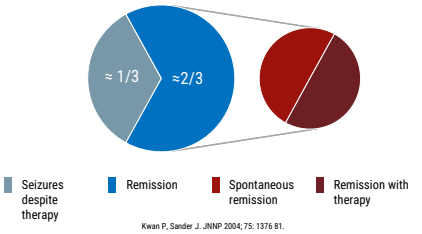



| | |
|---|---|
| **$Na^+$ channel blocker** | Carbamazepine, lamotrigine, phenytoin, zonisamide, felbamate*, oxcarbazepine, valproate*, rufinamide, topiramate, eslicarbazepine, lacosamide |
| **$Ca^{2+}$ channel blocker** | Topiramate, valproate, phenytoin, felbamate*, lamotrigine (?), oxcarbazepine (?), zonisamide |
| α2δ subunit | Gabapentine, pregabaline |
| "T" type channels | Etosuksimide |
| **SV2 protein** | Levetiracetam, Brivaracetam |
| **↓ Glutamate** | Topiramate, felbamate*, perampanel |
| **↑ GABA** | Benzodiazepines, tiagabine, vigabatrin*, phenobarbitone, primidone, valproate, topiramate |
| **Multiple mechanisms, unknown, metabolic effects** | Valproate*, ketogenic diet, other antiepileptics (?) |

Funded by the European Union
Grant ID: 101159214

## PROGNOSIS

The success of pharmacotherapy




Kwan P, Sander J. JNNP 2004; 75: 1376 81.

**Most patients with epilepsy have a very good prognosis!!**

- **Start low, go slow**
  - Start: low doses
  - Gradual increase at prescribed intervals
  - Until reaching therapeutic doses
- Advantage of **monotherapy** compared to polytherapy

## What clinicians want engineers to learn?

## Diagnostic pathway in epilepsy

No single test is enough

- Clinical history and witness/video description are the starting point
- EEG supports diagnosis, classification, and risk estimation, but is not a standalone truth test
- MRI epilepsy protocol may reveal structural epileptogenic lesions.
- Video-EEG is important for unclear events and presurgical evaluation
- Genetics, neuropsychology, PET/SPECT, and intracranial EEG are selected-case tools

## Epilepsy care is longitudinal

Why one note or one EEG is insufficient?

- Seizure frequency changes over time and is often incompletely documented
- Medication trials, adherence, side effects, injuries, and lifestyle factors matter
- Drug-resistant epilepsy is defined by treatment history, not a single EEG pattern
- Clinical decisions depend on longitudinal synthesis: diagnosis, treatment, safety, surgery, neurostimulation, and counseling

## AI/LLM cooperation ideas

## AI cooperation ideas

General AI in epilepsy

- **Seizure detection** from scalp EEG or intracranial EEG
- Interictal spike detection and quantification
- Seizure **forecasting and personalized risk models**
- **Multimodal monitoring:** EEG, video, ECG, accelerometry, electrodermal activity, wearables
- **Video-based semiology analysis** and nocturnal seizure detection
- Epileptogenic-zone localization and surgical outcome prediction

Slama et al.(2025); Bai et al. (2025); Wang et al. (2025)

Funded by the European Union
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## AI challenges in epilepsy

Why the problem is hard?

- Seizures are rare events within long recordings
- Patient-specific variability is high
- Labels may be uncertain or incomplete
- Artifacts and non-epileptic events can mimic seizures
- False alarms reduce usability; missed seizures reduce safety
- Models must generalize across devices, centers, montages, ages, and seizure types

## LLM cooperation ideas

Where LLMs are especially useful?

**Extract**
- Seizure semiology from patient and witness narratives
- Structure seizure diaries and summarize seizure frequency over time
- Antiseizure medication history, adherence, side effects, and prior treatment failures

**Identify**
- Patients with possible drug-resistant epilepsy for clinician review

**Prepare/ summarize**
- Epilepsy clinic follow-up and presurgical conference summaries
- EEG/MRI reports in context and generate patient-friendly explanations

## Example LLM output

From narrative to structured seizure data

**Input:**
"He suddenly stared, stopped responding, moved his lips, then his right arm stiffened. He was confused for 20 minutes."

- Structured output
  - should include onset, awareness, automatisms, lateralizing signs, duration, postictal state, witness source, uncertainty.
- Possible interpretation
  - focal impaired awareness seizure [but mimics and clinical context must be reviewed]
- Missing data
  - trigger, prior events, medication, injuries, EEG/MRI results, cardiac/ syncope history

## LLM safety in epilepsy

What the system should or should NOT do?

- Preserve source, temporality, uncertainty, and missing information
- Keep clinician review mandatory for diagnosis and treatment decisions

- Diagnose epilepsy from a narrative alone
- Convert "possible seizure" into "confirmed epilepsy"
- Overinterpret a normal or abnormal EEG
- Ignore mimics such as syncope or functional seizures

## Take-home messages

- Epilepsy is a clinical disorder, not only an EEG pattern
- Seizure semiology, witness history, EEG, MRI, medication response, and longitudinal course must be integrated
- **General AI** can support seizure detection, forecasting, multimodal monitoring, and surgical planning
- **LLMs** can structure narratives, diaries, medication histories, and reports, but should not autonomously diagnose epilepsy