Temporal lobe epilepsies: Current concepts

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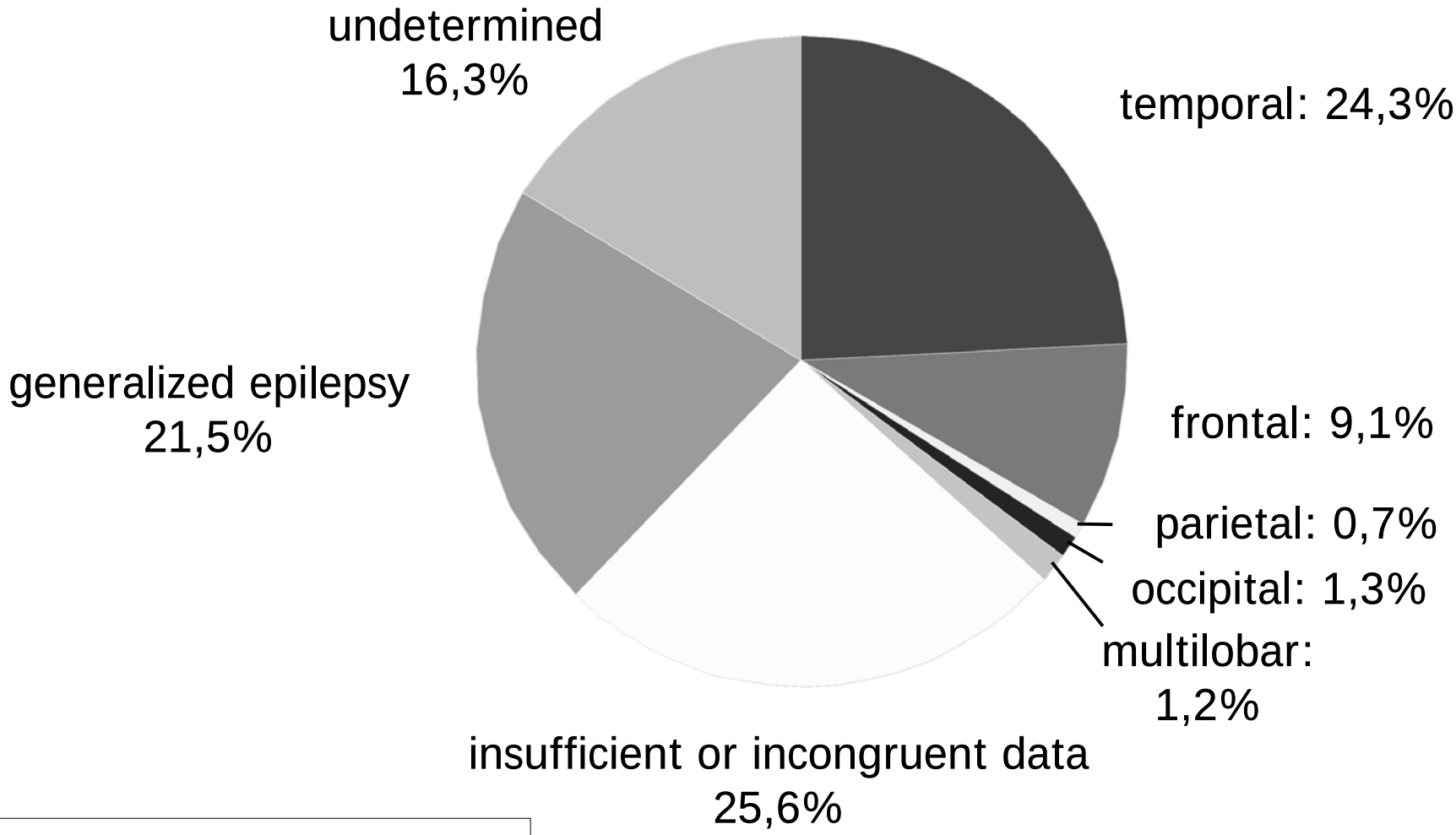
Outline

- epidemiology, course and prognosis
- clinical seizure semiology
- classification of temporal lobe epilepsies
- subtypes of temporal lobe epilepsies
- bilateral temporal lobe epilepsy
- special considerations: pseudo-temporal lobe epilepsy
- genetics

Temporal lobe epilepsies: Epidemiology, course and prognosis

Epidemiology - prevalence of TLE

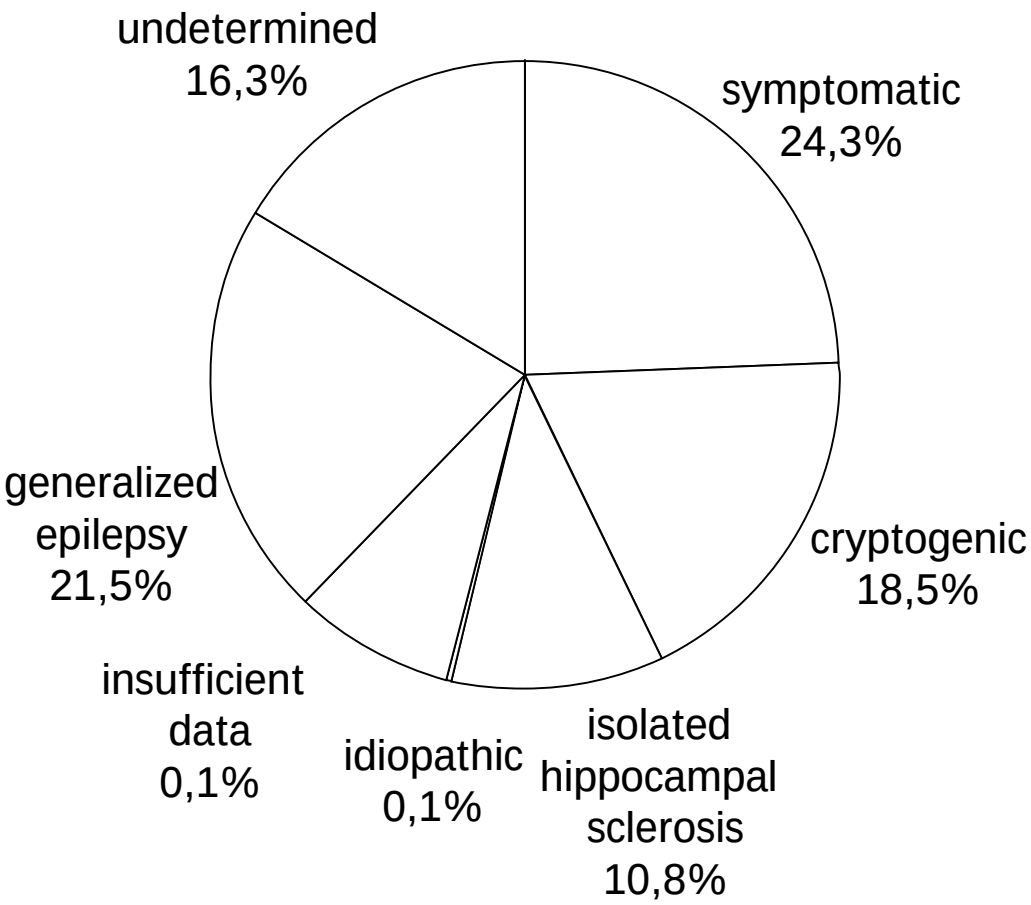
Semah et al. Neurology 1998;51:1256-1262



study population: n = 2200

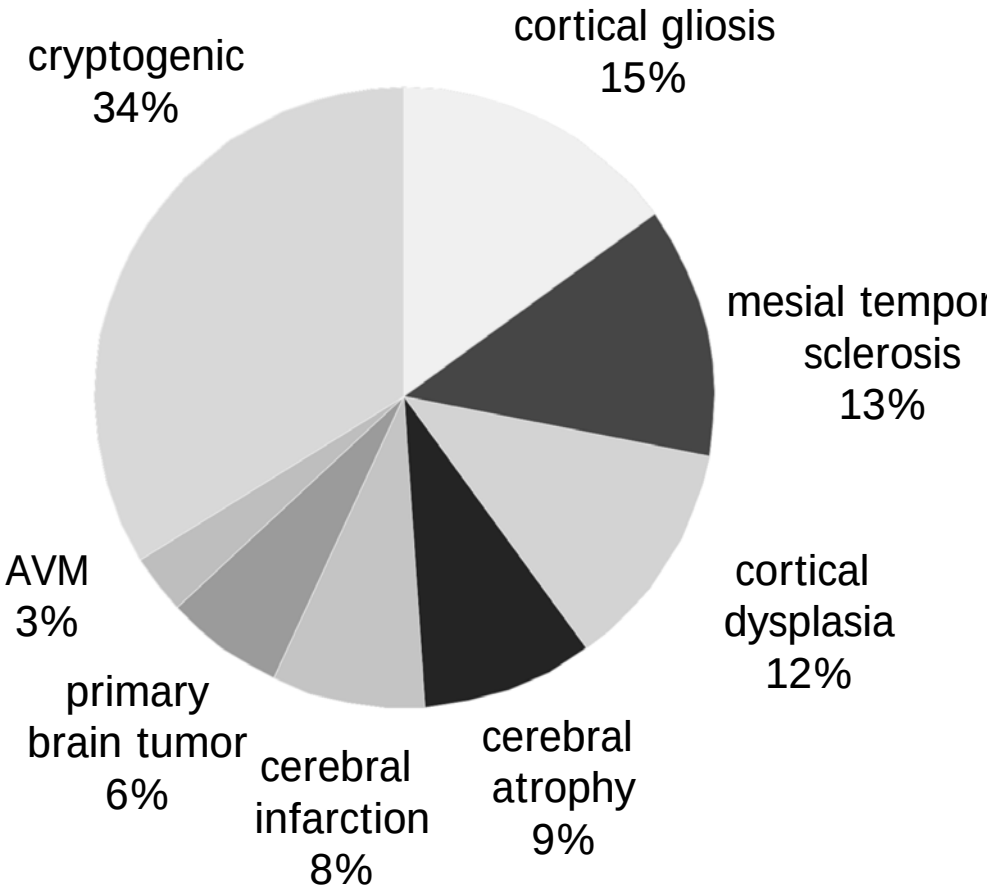
Epidemiology - prevalence of mesial TLE

Semah et al. Neurology 1998;51:1256-62



study population: n = 2200

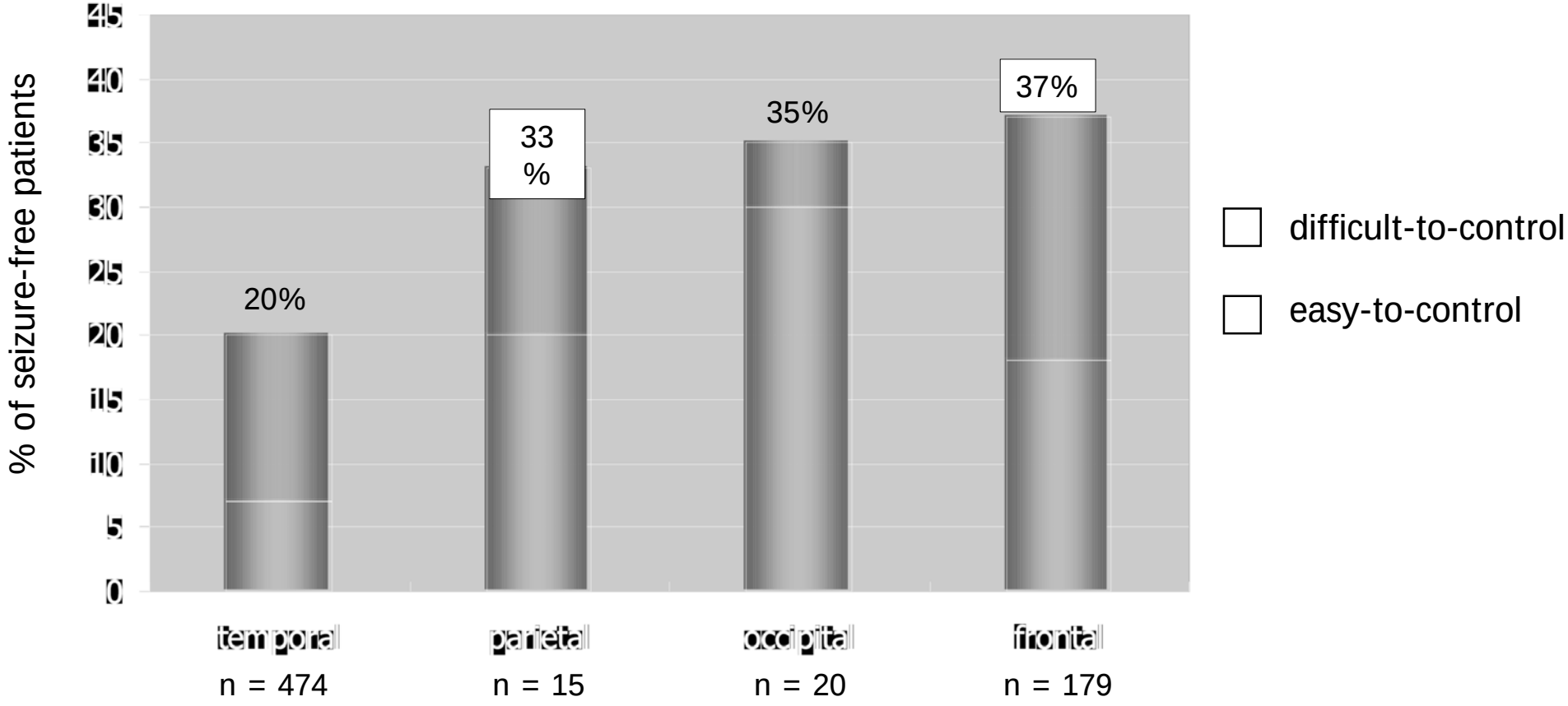
Stephen et al. Epilepsia 2001;42:357-62



study population: n = 550
focal epilepsies only!

Seizure control according to the location of the epileptogenic zone

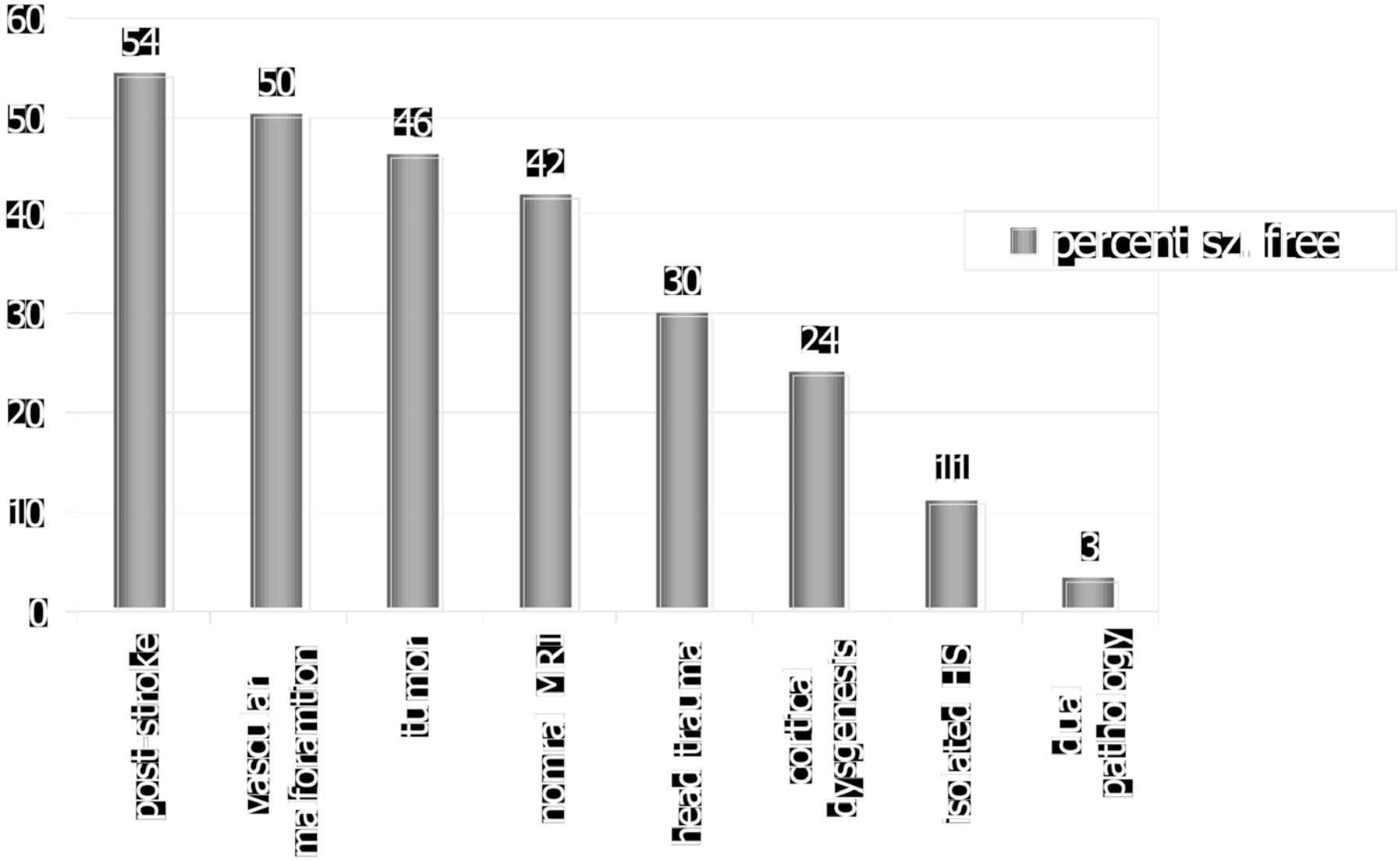
Semah et al. Neurology 1998;51:1256-1262



but: seizure control was not different in TLE patients without HS and extra-TLE patients

Seizure control according to etiology

Semah et al. Neurology 1998;51:1256-1262



Temporal lobe epilepsies: Clinical seizure semiology

Temporal lobe epilepsies: Seizure types

- seizure types in temporal lobe epilepsies
  - simple partial seizures
  - complex partial seizures
  - secondarily generalized tonic-clonic seizures
- complex partial seizures vs. temporal lobe seizures
  - complex partial seizures of temporal lobe origin
  - complex partial seizures caused by propagation of epileptic discharges into the temporal lobe, i.e. parietal and occipital lobe seizures => distinguish seizure onset zone vs. ictal symptomatogenic zone
  - frontal lobe complex partial seizures

Clinical seizure semiology in TLE

- auras
  - frequency: 22.5-83.0%
  - frequent: epigastric (40-70%); non-specific (difficult to describe); emotional – fear and anxiety (15-50%); illusion of familiarity and strangeness (20-30%); autonomous-vegetative
  - rare: olfactory, gustatory
  - loss of aura may indicate that seizure discharges become bilateral ?
- complex partial seizures
  - alteration of consciousness
  - negative motor symptoms
  - automatisms
  - positive motor symptoms
  - postictal symptoms
- secondarily generalized tonic-clonic seizures
  - frequency: 60%

Complex partial seizures in TLE (1)

- alteration of consciousness => complex partial seizures
  - reduction of reactivity and responsiveness
  - orientation reflex preserved or not
  - descriptive terms: ‘preserved’, ‘altered’, ‘clouded‘ consciousness, loss of consciousness
  - more profound alteration of consciousness ⇔ larger brain volume involved?
  - bilateral discharges not necessary, but frequently present
  - involvement of thalamus and upper brain stem structures?

Complex partial seizures in TLE (2)

- negative motor symptoms = arrest
  - frequent, but not specific
  - arrest with and without reactivity
  - increased tonus
- automatisms
  - ictal vs. postictal
  - reactive vs. de-novo
  - oral automatisms more frequent than gestural/manual
  - complex automatisms (e.g. running, pedaling) may indicate seizure spread to the frontal lobe

Complex partial seizures in TLE (3)

- positive motor symptoms
  - clonic or clonic/tonic facial-brachial motor symptoms
  - clonic head and eye version
  - dystonic posturing of the upper extremity
  - asymmetric tonic limb posturing (‘figure 4 sign’)
  - secondary tonic-clonic generalization
- postictal symptoms
  - cognitive impairment
  - mood changes
  - memory deficits
  - language deficits

Clinical seizure lateralization

Contralateral signs

- unilateral dystonic posturing
- unilateral mouth deviation
- unilateral clonic activity (face or hand)
- version
- unilateral tonic extension of one upper extremity at the onset of generalization (figure 4 sign)
- ictal hemiparesis
- postictal hemiparesis

Ipsilateral signs

- unilateral upper extremity automatisms
- non-versive early head turning
- postictal nosewiping
- asymmetric ending of the clonic phase at the end of a generalized tonic-clonic seizure
- unilateral eye lid blinking
- (peri-ictal headache)
- (lateral tongue biting)

Clinical Seizure Lateralization

seizure-onset in the non-dominant hemisphere

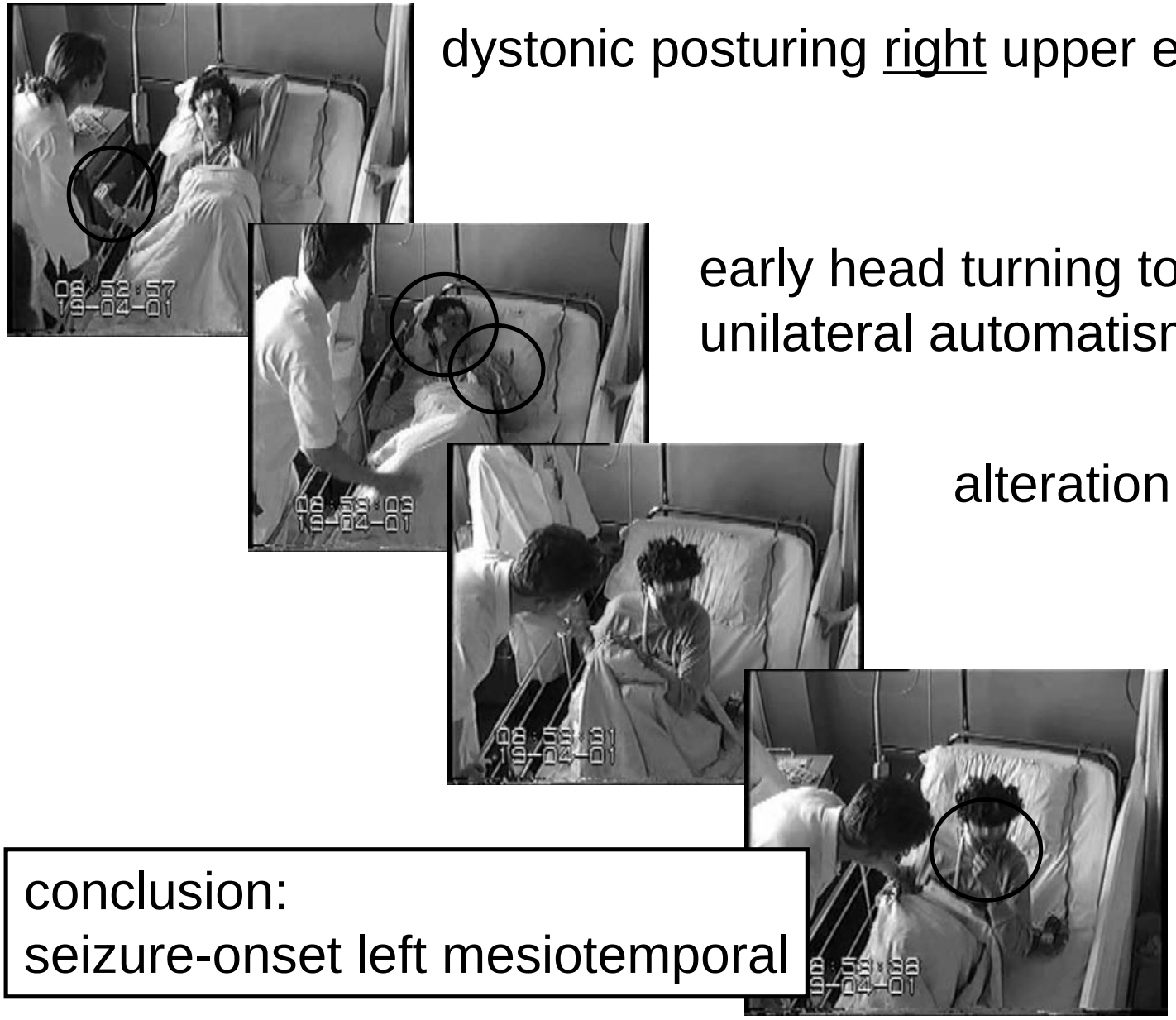
- preserved ictal speech
- automatisms with preserved responsiveness
- ictal vomiting/retching
- ictal spitting
- peri-ictal urinary urge
- peri-ictal water drinking
- postictal coughing
- ictal smile
- peri-ictal crying

seizure-onset in the dominant hemisphere

- postictal dysphasia

Clinical seizure semiology

Clinical seizure semiology



dystonic posturing right upper extremity

early head turning to the left
unilateral automatisms left upper extremity

alteration of consciousness

postictal nosewiping
left upper extremity

conclusion:
seizure-onset left mesiotemporal

Temporal lobe epilepsies: Classification

Temporal lobe epilepsies - classification

- etiology
  - idiopathic
  - symptomatic
  - cryptogenic
- location of the seizure onset zone
  - ILAE 1989: medial vs. lateral
  - hippocampus
  - amygdala
  - temporal pole
  - lateral neocortex
  - diffuse
- bilaterality
  - unilateral vs. bilateral

Temporal lobe epilepsies - classification

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  - diffuse

- bilaterality
  - unilateral vs. bilateral

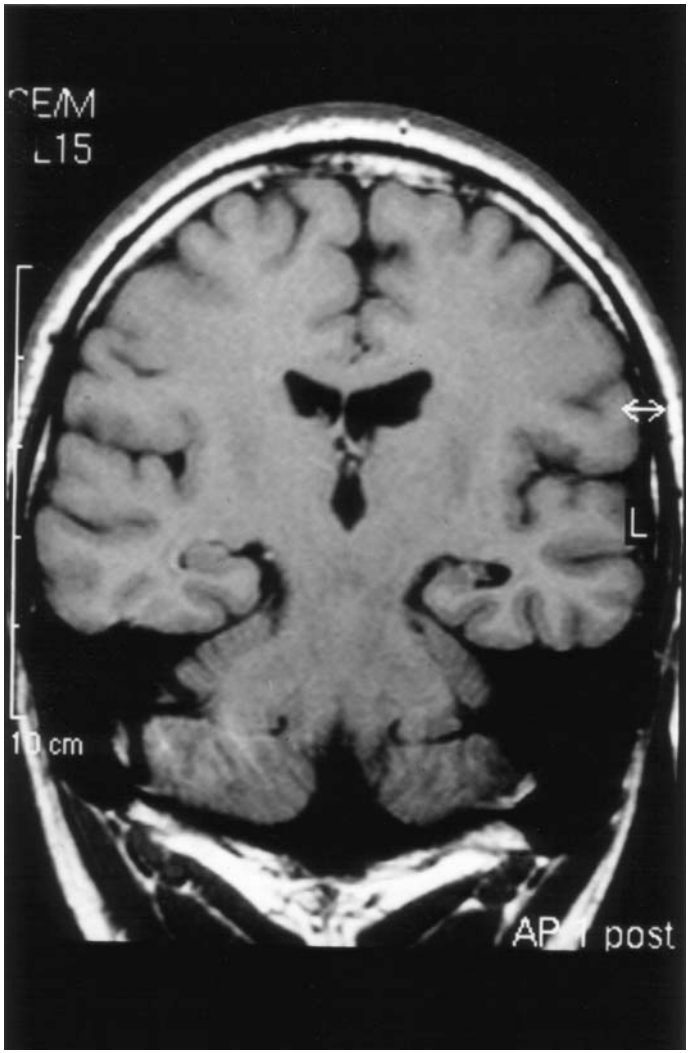
Temporal lobe epilepsies - etiology

- mesial temporal lobe epilepsy - symptomatic
  - hippocampal atrophy/sclerosis
- lesional temporal lobe epilepsy - symptomatic
  - structural lesion other than hippocampal atrophy/sclerosis
  - dual pathology <=> extrahippocampal lesion associated with hippocampal atrophy/sclerosis
- non-lesional temporal lobe epilepsy - cryptogenic
  - normal MRI-scan and/or histology
- familial temporal lobe epilepsies - idiopathic

Mesial temporal lobe epilepsy (MTLE)

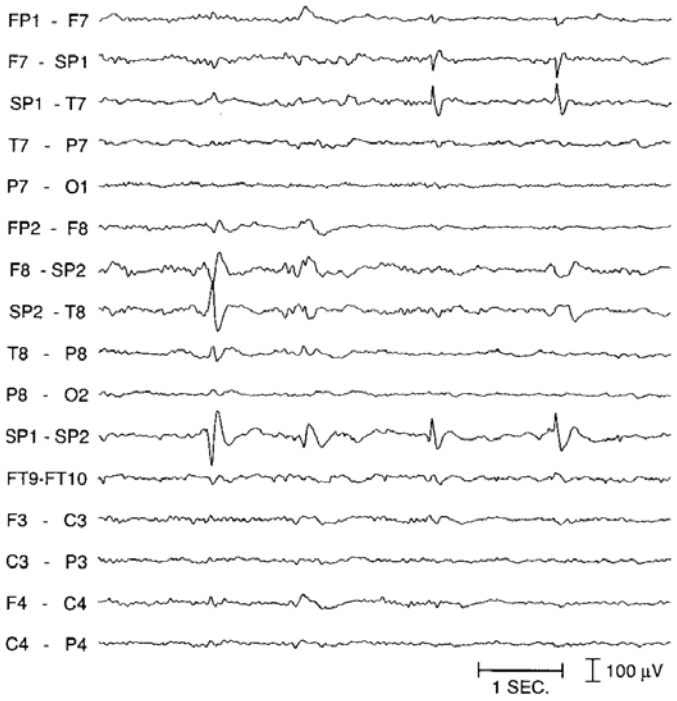
Mesial temporal lobe epilepsy

- most frequent epilepsy syndrome
- history
  - initial precipitating incident (IPI; complicated febrile convulsions, trauma, hypoxia, intracranial infection before the age of 5 years)
  - seizure-free interval (latent period)
  - seizure-onset without fever: second half of the first decade or later => initially good response to antiepileptic drug treatment (silent period)
  - seizures recur and turn out to be medically refractory in 30-50% of patients
- pathologic substrate = mesial temporal sclerosis (MTS)



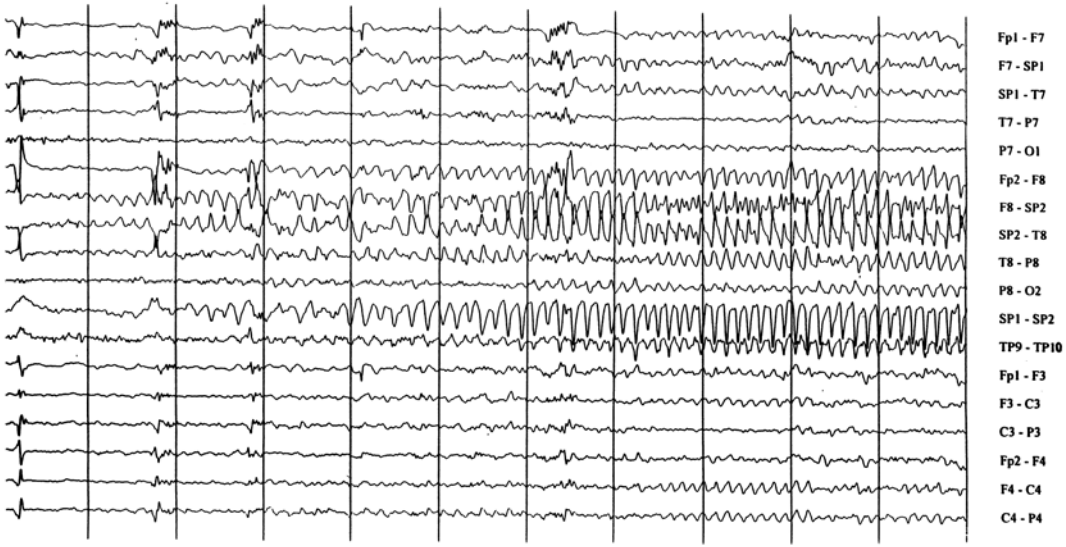
Mesial Temporal Lobe Epilepsy - EEG

interictal EEG



- anterior temporal spikes (maximum FT9/FT10 resp. Sp1/Sp2)
- intermittent (rhythmic) slow activity, regional temporal

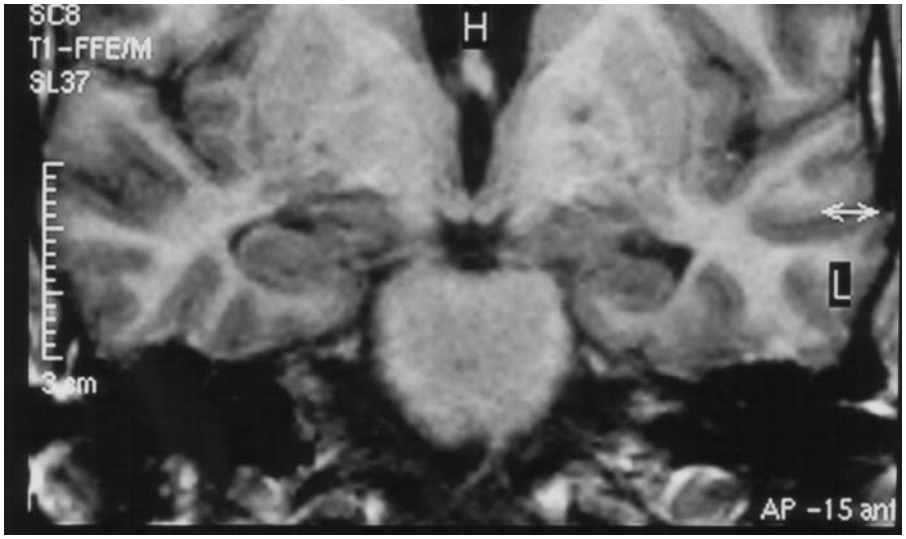
ictal EEG



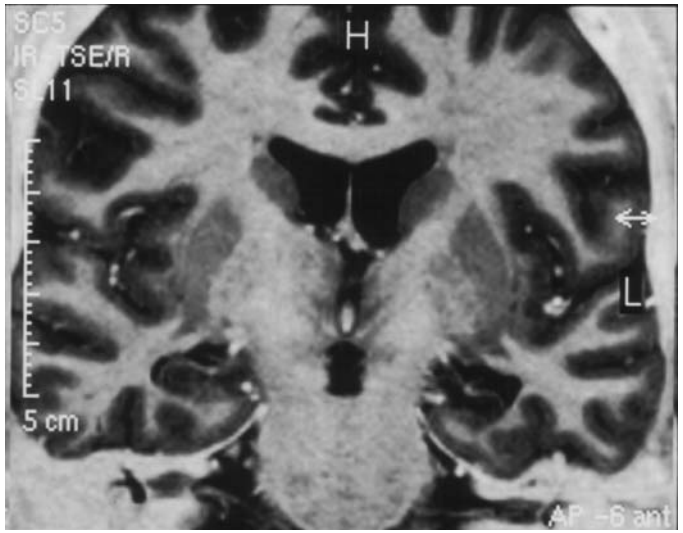
- rhythmic alpha, theta or delta activity localized to the temporal lobe (‚temporal recruiting rhythm‘)

Mesial Temporal Lobe Epilepsy - MRI

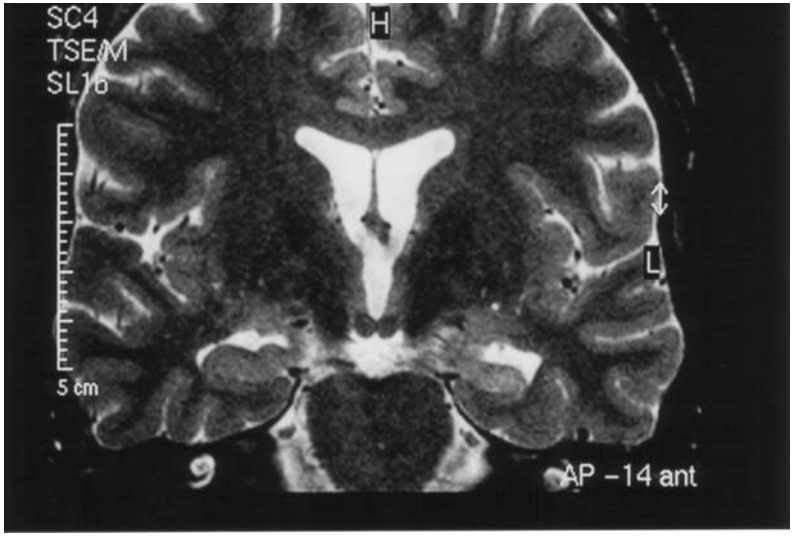
T1



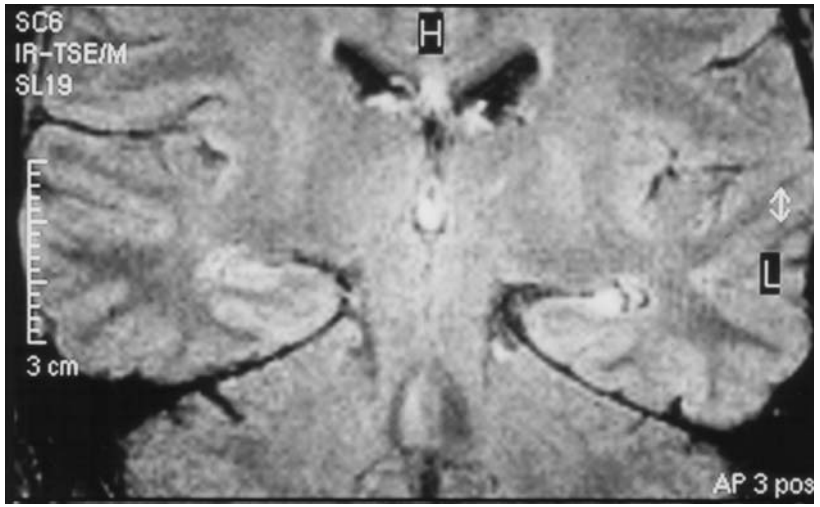
IR



T2

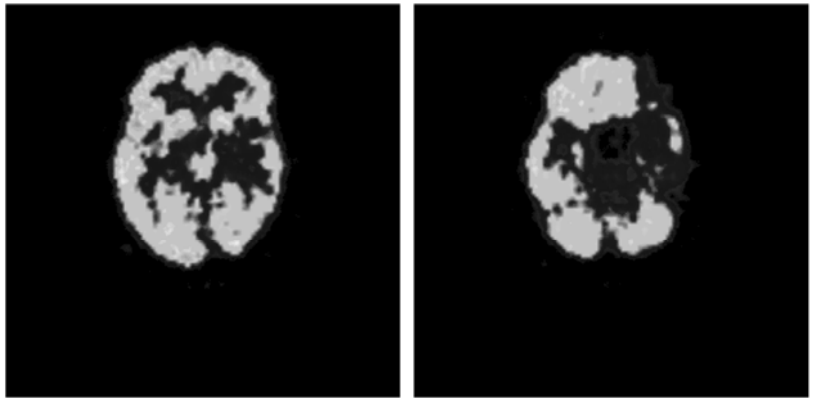


FLAIR

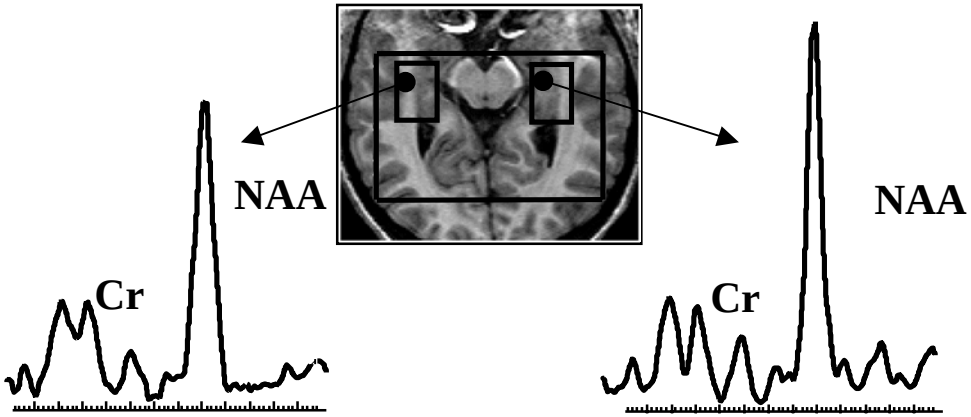


MTLE - functional deficits

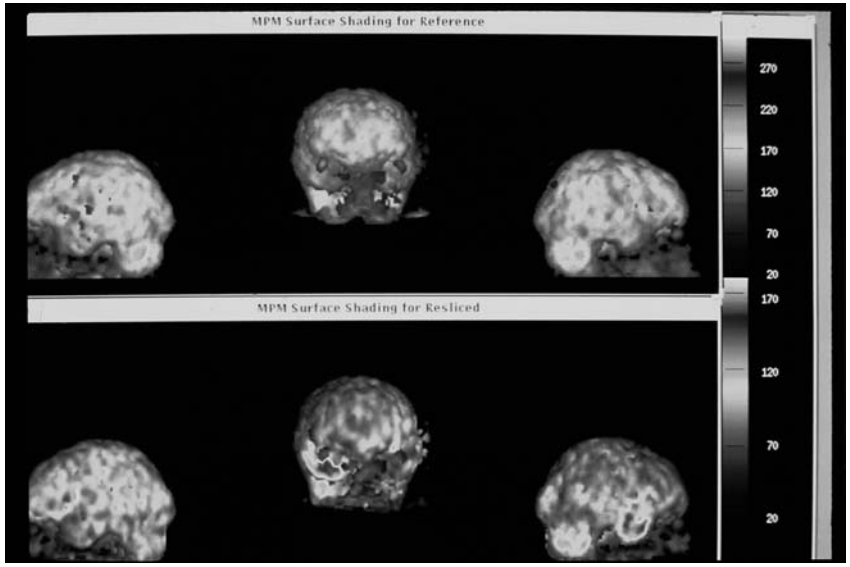
PET



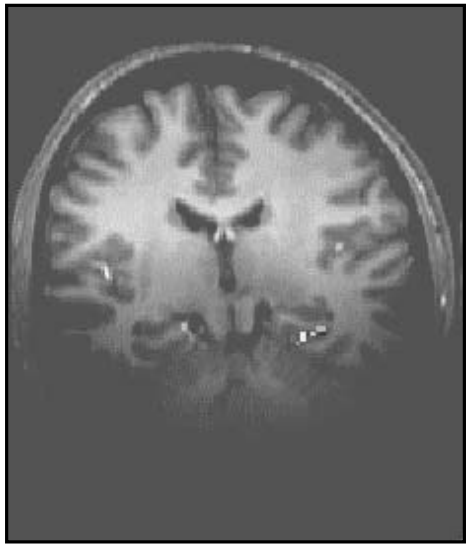
MRS



SPECT



neuropsychology / functional MRI



Lesional temporal lobe epilepsy

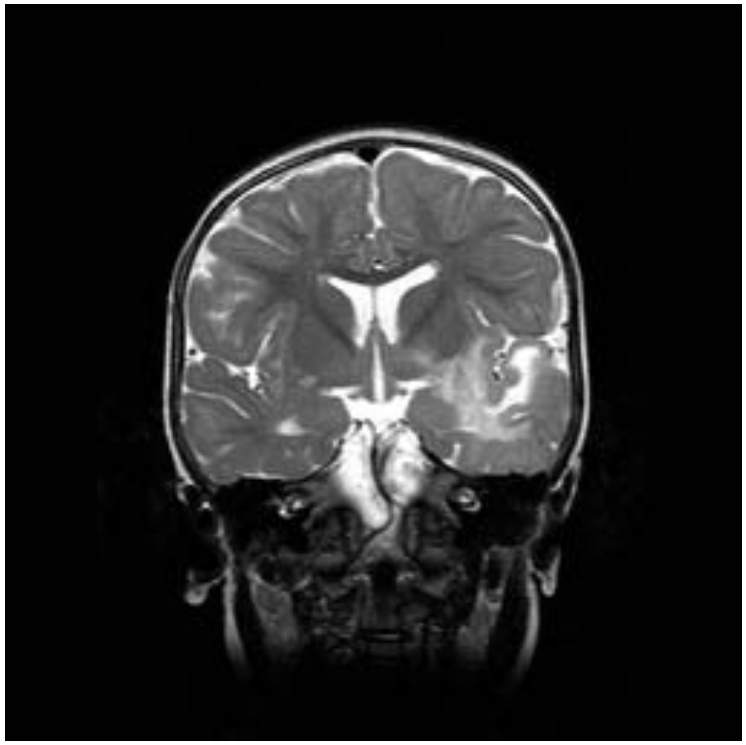
Lesional temporal lobe epilepsy

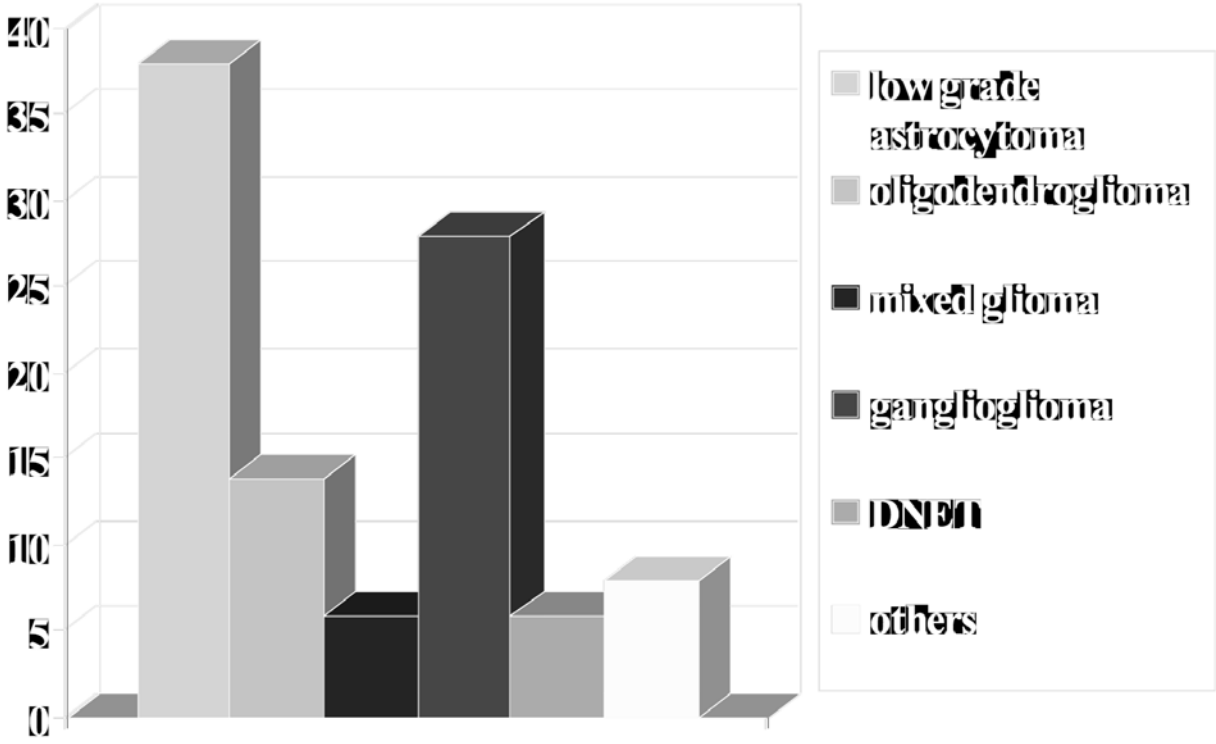
- epidemiology
  population based series: 5.2%; surgical series: 15-58%; MRI series: 34-45%
- primary brain tumors
- neuronal migration disorders
- vascular malformations
- others

  cystic lesions (porencephalic cysts; arachnoid cysts), infectious lesions (postencephalitic lesions; neurocysticercosis, tuberculoma); encephalomalacia; posttraumatic lesions

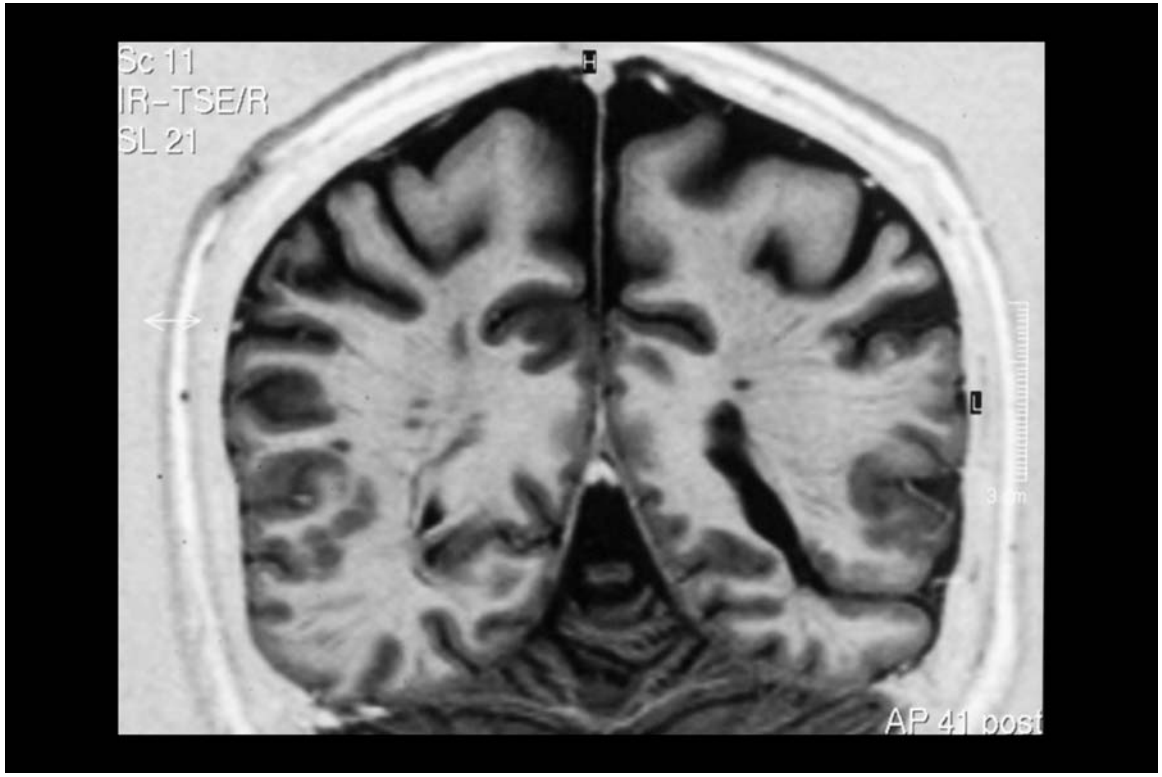
Lesional Temporal Lobe Epilepsies – Frequency of Tumor Types in Chronic Epilepsy

Pooled Data from 4 Epilepsy Surgery Centers (Cleveland, New Haven, Rochester, Bonn) n=203

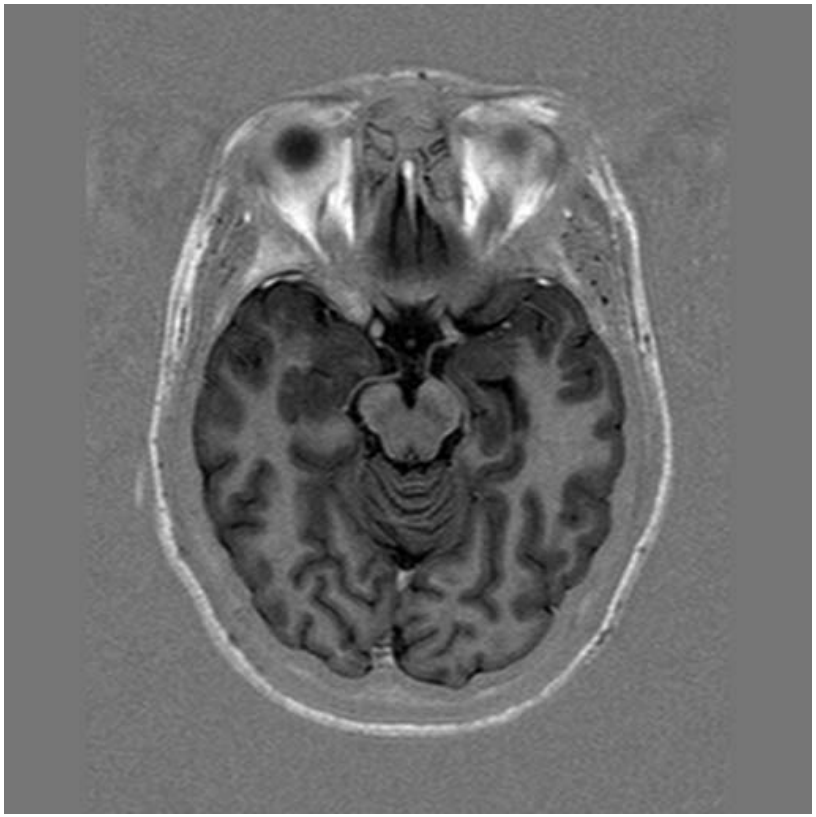




Disorders of cortical development



schizencephaly



focal cortical dysplasia

intrinsic epileptogenicity

Temporal lobe epilepsies – dual pathology

- extrahippocampal lesion plus hippocampal atrophy /sclerosis
- frequency
  - 5-20% of patients with refractory epilepsy referred for surgical evaluation
  - quantitative MRI-based studies: 15%
- types of extrahippocampal lesions
  - most frequent in cortical dysgenesis and other congenital lesions or lesions acquired early in life (gliotic lesions acquired in early childhood, vascular malformations) $\Rightarrow$ special vulnerability of the hippocampus early in life
  - less frequent in tumors and contusions/infarcts
- epilepsy surgery
  - removal of lesion and atrophic hippocampus
  - outcome independent of degree of hippocampal atrophy and type of lesion

Li et al. Neurology 1997;48:437-44
Li et al. Brain 1999;122:799-805
Salanova et al. Acta Neurol Scand 2004;109:126-131

Non-lesional temporal lobe epilepsy

Non-Lesional Neocortical Temporal Lobe Epilepsy (NLTLE) - Definition

- definition
  - cryptogenic temporal lobe epilepsy
  - absence of structural lesion on MRI scan
  - normal histological examination
- seizure-onset zone
  - often lateral, neocortical as evidenced from invasive recordings
  - term: non-lesional neocortical temporal lobe epilepsy (NCTLE)
- problems
  - MRI scan => constant improvement, but some patients with normal MRI scans still show hippocampal sclerosis on histologic examination
  - definition based on histologic examination => restricted to surgical patients, can be applied only retrospectively

Differentiation of NLTLE from MTLE

	MTLE	NLTLE
febrile convulsions	frequent	rare
seizure-free interval	frequent	rare
seizure onset	early	late
seizure semiology	epigastric auras, early oral automatisms, manual automatisms, leg movements, contralateral dystonic posturing, searching movements, body shifting, hyperventilation, postictal cough	experiential and auditory auras, early motor involvement of the contralateral upper extremity without oral automatisms
PET hypometabolism	medial and lateral	lateral
neuropsychology	material-specific memory deficits	no memory deficits

Differences in clinical semiology between seizures arising from the mesial vs. lateral temporal lobe

- dystonic posturing: MTLE > NTLE
- facial grimacing / twichting: earlier in NTLE than in MTLE

O'Brien et al. Brain 119: 2133-41 (1996)
Pfänder et al. Epileptic Disord 4: 189-95 (2002)

- early oral automatisms: hippocampal > extrahippocampal
- early motor involvement of the contralateral upper extremity without oral automatisms: extrahippocampal > hippocampal

Gil-Nagel und Risinger. Brain 120: 183-92 (1997)

- oral and manual automatisms; leg movements; dystonic posturing; body shifting; hyperventilation; postictal cough/sigh: MTLE > NTLE

Foldvary et al. Neurology 49: 757-63 (1997)

Differences in auras between seizures arising from the mesial vs. lateral temporal lobe

- no difference between mesial and lateral-neocortical onset seizures

O'Brien et al. Brain 119: 2133-41 (1996)

Foldvary et al. Neurology 49: 757-63 (1997)

- epigastric auras => hippocampal seizure onset
- experiential auras => extrahippocampal seizure-onset

Gil-Nagel und Risinger. Brain 120: 183-92 (1997)

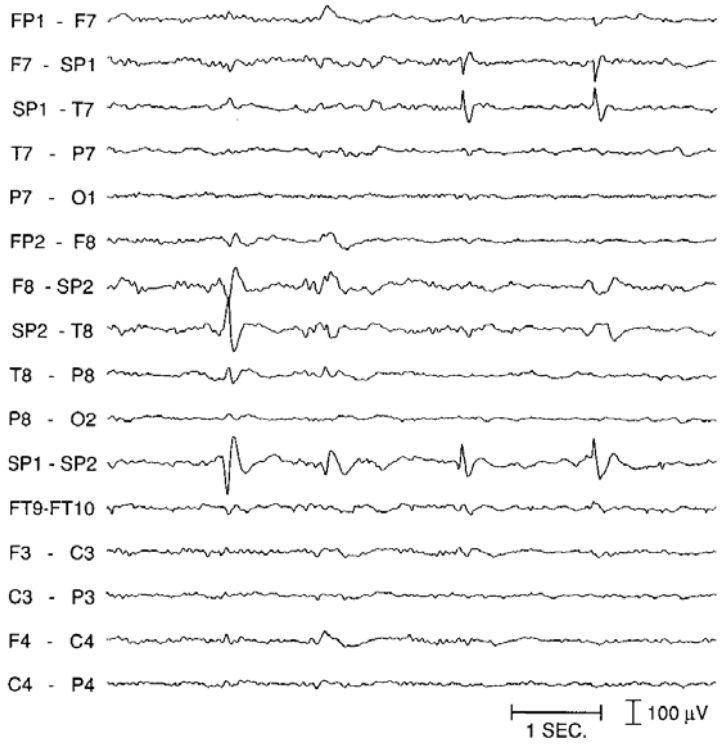
Pfänder et al. Epileptic Disord 4: 189-95 (2002)

Bilateral temporal lobe epilepsy

Bilateral Temporal Lobe Epilepsies: Markers of Bitemporal Affection

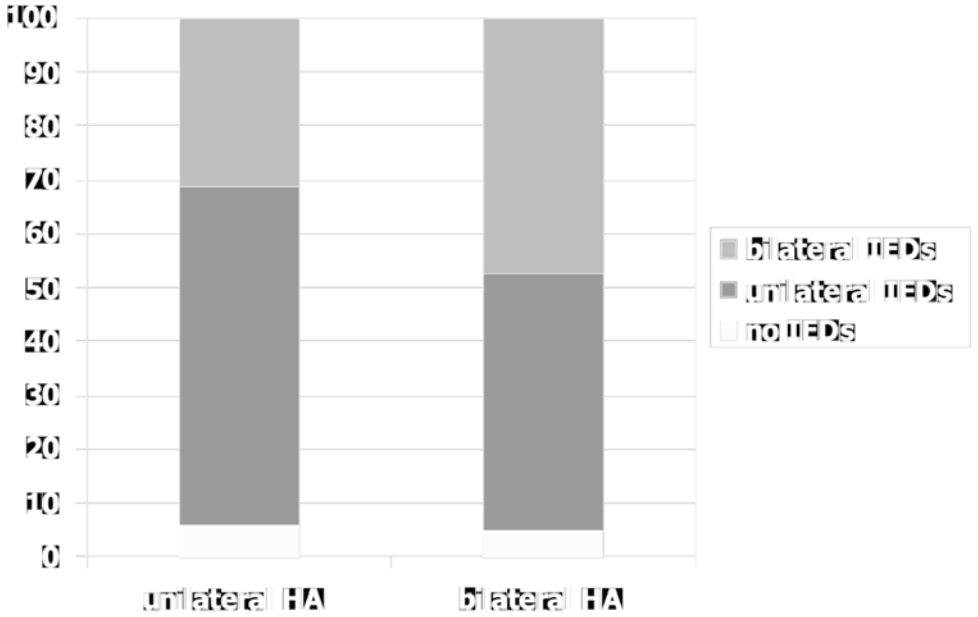
- bitemporal interictal spikes
  - definition: <90% of spikes over the more affected temporal lobe
  - 8-42 (61)% of patients
  - unfavorable prognostic sign in epilepsy surgery patients
- bitemporal ictal EEG changes
  - independent seizures from both temporal lobes
  - different or identical clinical seizure semiology
- bitemporal functional deficits
  - slowing on EEG; SPECT; PET; MR-spectroscopy; neuropsychology
- bitemporal structural alterations
  - bilateral hippocampal volume loss on MRI (volumetric studies)
  - autopsy studies: 41-56% (Margerison. Brain 1966;89:499-530)

Bilaterality of structural changes vs. IEDs



MRI-volumetry vs. IEDs

Gambardella. Epilepsia 1995;36:122-129



➔ no strict correlation between different markers of bilaterality

Temporal lobe epilepsies: Special considerations

Pseudotemporal lobe epilepsies

- lesions at a distance from the temporal lobe leading to epileptiform discharges which appear to arise from temporal structures
  - Fish et al. Neurology. 1991;41:1781-4
  - Palmini et al. Epilepsia. 1993;34:84-96
- disorders of cortical development
  - double cortex syndrome (Bernasconi et al. Epilepsia. 2001;42:1124-9)
  - periventricular nodular heterotopia (Li et al. Ann Neurol. 1997;41:662-8)
  - hypothalamic hamartoma
- non-lesional focal epilepsy with focal anterior and inferomesial temporal epileptic discharges and posterior temporoparietal clinical symptoms
  - Aghakhani et al. Epilepsia. 2004;45:230-6

➔ poor outcome after temporal lobe resections despite EEG abnormalities localized to the temporal lobe

➔ temporal localization of EEG abnormalities does not necessarily imply origin of seizures within temporal structures

Temporal lobe epilepsies: Genetics

Temporal lobe epilepsies – genetics

- TLE as part of autosomal dominant epilepsy syndromes = familial TLE

- susceptibility genes

  significant association of epilepsy with a particular polymorphism within a gene?

Familial temporal lobe epilepsy subtypes

- autosomal dominant partial epilepsy syndrome with auditory features (ADPEAF)

  Ottman et al. Nat Genet 1995;10:56-60

- familial mesial temporal lobe epilepsy

  Berkovic et al. In: Wolf P ed. Epileptic Seizures and syndromes. London: John Libbey, 1994:257-63

  Berkovic et al. Ann Neurol 1996;40:227-35

- familial partial epilepsy with variable foci (FPEVP)

  Scheffer et al. Ann Neurol 1998;44:890-9

- partial epilepsy with pericentral spikes (PEPS)

  Kinton et al. Ann Neurol 2002;51:740-9

Susceptibility genes

- prodynorphin gene
  encodes for dynorphin = anticonvulsant peptide

  Stögmann et al. Ann Neurol 2002;51:260-3
- interleukin-1β (IL-1β), IL-1α and IL-1 receptor antagonist genes
  encode for proinflammatory cytokines that modulate neurotoxic neurotransmitters

  Kanemoto et al. Ann Neurol 2000;47:571-4

  Tsai et al. Arch Pediatr Adolesc Med 2002;156:545-8
- apolipoprotein E (APOE) ϵ4 allele

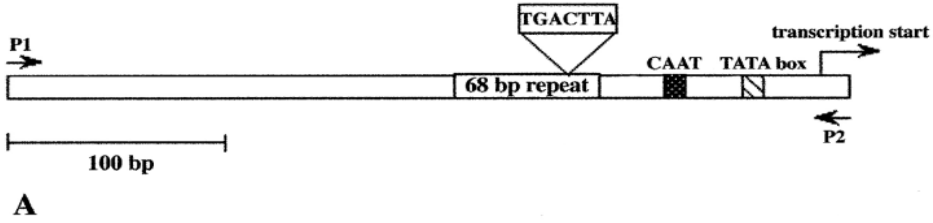
  promotes deposition of β-amyloid, damage repair is compromised in its presence

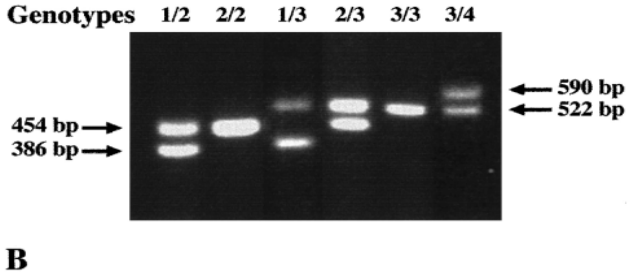
  Briellmann et al. Neurology 2000;55:435-7
- polymorphism of GABA (B) receptor 1 gene
  encodes for GABA, association between TLE and G1465A polymorphism

  Gambardella et al. Epilepsia 1999;40:1804-7

Dynorphin in temporal lobe epilepsy

- family of opioid peptides => activates κ-receptors
- highly expressed in dendate granular cells
- inhibits excitatory synaptic transmission = endogenous anticonvulsant peptide





Stögmann et al. Ann Neurol 2002;51:260-3

- PDYN promotor low-expression L-alleles ⇒ increased risk for temporal lobe epilepsy in patients with a family history for seizures
- L-homozygotes display a higher risk for secondarily generalized seizures and status epilepticus

Conclusions

- TLE is frequent and especially MTLE is frequently intractable epidemiology
- clinical seizure semiology depends on location and not on etiology
- classification
  - etiology versus seizure onset zone
  - combination of etiologies
  - combination of seizure onset zones
- both temporal lobes are a continuum
- genetic aspects
  - classification
  - genetic implications on course and prognosis

Thank you!