Epilepsy Syndromes

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EPILEPSY SYNDROMES - epileptic disorders characterized by **specific clusters of signs & symptoms (semiologies), EEG abnormalities, etiologies, comorbidities**

- syndromes, by definition, are empirical and artificial.
- modern diagnostic techniques including MRI and genetic testing allow precise diagnosis of epilepsy causes, therefore identification of syndromes is less important than it once was.
- defining epileptic syndrome was* (and sometimes still is**) a priority - major implications for diagnostic evaluation, treatment, genetic counseling, and prognosis.
- most of these syndromes have **numerous etiologies** (only few have been defined as specific diseases!).
  *for many decades, classic epileptology assumed that identification of an epilepsy syndrome was the diagnostic gold standard.
  **there are innumerable publications on study treatment and prognosis for different epileptic syndromes.

### CLASSIFICATION

**Step 1 – by seizure onset**

**GENERALIZED epilepsy syndromes** - seizures with initial activation of *both cerebral hemispheres.*

**LOCALIZATION-related (s. FOCAL) epilepsy syndromes** - seizures originate from *localized cortical region.*

**Step 2 – by seizure cause** - IDIOPATHIC, SYMPTOMATIC, CRYPTOGENIC.

**Step 3 – seizure subtypes** according to *patient's age.*

- in localization-related epilepsies – also by *anatomic location* of ictal zone.

**I. IDIOPATHIC epilepsy syndromes** (focal* or generalized**):

- A. Autosomal dominant **temporal lobe epilepsy***
- B. **Benign partial epilepsy of childhood***
- C. **Childhood/juvenile absence epilepsy (pyknolepsy)**** - 3-4% of all seizure disorders (15-20% of children epilepsies)
- D. **Juvenile myoclonic epilepsy**** (incl. grand mal seizures on awakening) – 4-10% of all epilepsies.
- E. **Benign myoclonic epilepsy of infancy****
- F. **Benign neonatal convulsions****; familial, nonfamilial (idiopathic)
- G. Autosomal dominant **nocturnal frontal lobe epilepsy** *
- H. Generalized epilepsy with **febrile seizures plus****
- I. Idiopathic epilepsy, otherwise unspecified

- most patients have normal neurological examinations and normal intelligence.
- presumably genetic basis.

**II. CRYPTOGENIC / SYMPTOMATIC epilepsy syndromes** (focal* or generalized**):

- A. **Temporal lobe epilepsy*** - at least 40% of all epilepsies in adults!
B. Frontal lobe epilepsy*
C. West’s syndrome (infantile spasms)**
D. Lennox-Gastaut syndrome** - 2-3% of childhood epilepsies
E. Epilepsia partialis continua:
   1) Rasmussen syndrome (encephalitic form)
   2) restricted form
F. Post-traumatic epilepsy
G. Early myoclonic encephalopathy
H. Epilepsy with myoclonic astatic seizures**
I. Epilepsy with myoclonic absences**
J. Acquired epileptic aphasia (Landau-Kleffner syndrome)
K. Other symptomatic epilepsies, otherwise unspecified

III. Other epilepsy syndromes of UNCERTAIN or MIXED classification:
A. Febrile seizures - most common (≈ 66%) seizure disorder in children! (occur in 2-5% of general children population)
B. Autoimmune epilepsies
C. Neonatal seizures
D. Reflex epilepsy
E. Situation-related seizures (Gelegenheitsanfälle)
F. Adult nonconvulsive status epilepticus
G. Other unspecified

LOCALIZATION-RELATED (FOCAL) EPILEPSY SYNDROMES

TEMPORAL LOBE EPILEPSY (TLE)

A. Mesial TLE, MTLE (most common!* - seizures arise in mesial temporal lobe structures (hippocampus, amygdala, parahippocampal gyrus).
B. Neocortical TLE.

*MTLE is the most common focal epileptic disorder in adults, with approximately 40% of cases refractory to medical therapy

EPIDEMIOLOGY

- hippocampal sclerosis is #1 surgical pathology among adults (44.5% surgical specimens; only 15% in children)

ETIOLOGY, PATHOLOGY

MESIAL TEMPORAL (S. HIPPOCAMPAL) SCLEROSIS (MTS)
- most common (60-80%) pathological substrate of TLE - highly selective (segmental) loss of specific neuron populations within hippocampus with concomitant astrogliosis:

| > 30% pyramidal cell loss in CA1 and / or CA4, with relative sparing of CA2 + severe astrogliosis |

N.B. segmental hippocampal neuron loss can be also observed in other pathologic conditions, including dementia, aging, ischemia, and neurodegeneration, but the patterns of neuronal cell loss may differ and usually also involves the subiculum.

- **marked neuronal loss** in CA1 (Sommer's sector), CA3, CA4, dentate gyrus (primarily hilar polymorphic region) → *secondary gliosis* and *reactive synaptogenesis*;
  - pyramidal cells in CA2, subiculum, entorhinal cortex, and temporal neocortex are relatively spared.
  - 20-30% cases have coexistent *extralimbic lesions* (hamartomas, cortical dysplasia, heterotopic grey matter).
- **neuronal loss** in CA1 has *gradient from anterior to posterior* (if marked cellular loss is found at most posterior extent of hippocampal resection - high correlation with persistent seizures).
- neuron loss is always associated with a severe pattern of astrogliosis, defined by a dense meshwork of glial fibrillary acidic protein (GFAP)–positive processes:
- pathophysiology: selective loss of *mossy cells* and *neurons containing somatostatin and neuropeptide Y* → deafferentation of normally powerful GABA inhibitory neurons within dentate gyrus, rendering them nonfunctional → disinhibited granule cells of dentate gyrus (respond with abnormal synchronous bursts to cortical stimuli) → subclinical electrographic seizures → further damage to vulnerable cell populations (self-enhancing cycle of cell loss) → clinical seizures.
  - mossy-fiber sprouting: mossy fibers (axons of dentate granule cells) project into hilar polymorphic region; as neurons in hilar polymorphic region are lost, their feedback projection into dentate granule cells degenerates; such denervation (due to loss of hilar projection) induces sprouting of neighboring mossy fiber axons → formation of *monosynaptic recurrent excitatory collaterals* (increased net excitatory drive of dentate granule neurons).
- MTLE is associated with *network rearrangement* within, but not restricted to, temporal lobe ipsilateral to onset of seizures.

Hippocampus: **A – normal; B – mesial temporal sclerosis**: loss of pyramidal cells in CA1 *(curved arrow, left)*, CA4 *(straight arrow, right)*, and hilus (H) of dentate gyrus; CA2 (pyramidal cells lying to left of arrow on right) and granule cell layer (G) are characteristically less affected:
**ILAE classification**


**HS ILAE type 1, s. classic or complete patterns** (60-80%) - severe neuronal cell loss and gliosis predominantly in **CA1 and CA4**; often associated with a history of initial precipitating injuries before age 5 years, with early seizure onset, and **most favorable postsurgical seizure control**.

**HS ILAE type 2** (5-10%) - predominantly in **CA1**; less favorable outcome than type 1.

**HS ILAE type 3, s. end folium sclerosis** (4-7.4%) - predominantly in **CA4**; less favorable outcome than type 1.

**no-HS** (20%) - normal content of neurons with reactive gliosis only.

GFAP-immunoreactivity patterns counterstained with hematoxylin:
A. **no-HS**: single reactive astrocyte was immunolabeled in this CA1 region, whereas many other astrocytes did not express detectable levels of GFAP.
B. **ILAE HS type 1**: moderate reactive astrogliosis in CA1 region with only slight decrease of neuronal density.
C. **ILAE HS type 1**: severe fibrillary astrogliosis with a dense meshwork of GFAP-labeled fine processes in a sclerotic CA1 region.
A. **ILAE HS type 1**: pronounced preferential pyramidal cell loss in both CA4 and CA1 sectors. Damage to sectors CA3 and CA2 is more variable, but frequently visible. Note variable cell loss also in the dentate gyrus, with abundant granule cell loss in the internal limb (DGi) in this sample, and a transition with preservation of cells in the subiculum (SUB).

B. **ILAE HS type 2**: neuronal loss primarily involving CA1 compared with other subfields.

C. **ILAE HS type 3**: restricted cell loss mostly in CA4.

D. **no-HS**: no hippocampal sclerosis, gliosis only – no significant cell loss in any of the hippocampal subregions.
3T T2 MRI findings (volumetric loss is severe in ILAE HS type 1, moderate in ILAE HS type 2, but virtually not detectable in ILAE HS type 3):
A. ILAE HS type 1.
B. ILAE HS type 2.
C. ILAE HS type 3.

**NEOCORTICAL TLE**
- etiologies:
  1) low-grade primary brain tumors (10-15%), most commonly – *GANGLIOGLIOMA*.
  2) areas of cortical dysplasia (10-15%)
  3) cavernomas
• may be associated with hippocampal atrophy!

**CRYPTOGENIC TLE**
- temporal lobe is identified as putative epileptogenic region primarily based on intracranial electrophysiology.

**CLINICAL FEATURES**
• onset ranges *latter half of first decade ÷ early adulthood*.
• common family history of epilepsy.
• many cases begin several years after complicated febrile seizures (!), head trauma, or CNS infection.
Patients have history of higher incidence of *complicated febrile seizures* than in other types of epilepsy.

- seizures often remit for several years until adolescence or early adulthood.
- common interictal behavioral disturbances (esp. depression).

1. **COMPLEX PARTIAL SEIZURES** (50% experience secondarily generalized TCS): see p. E1 >>
   
   N.B. 70-80% of all complex partial seizures arise in **TEMPORAL LOBE**!
   
   - most patients have aura:
     - aura in *mesial TLE* – visceral (esp. epigastric) sensations, olfactory / psychic phenomena (fear, anxiety) → synonyms *psychomotor epilepsy, limbic epilepsy*.
     - aura in *neocortical TLE* – auditory hallucinations, complex visual phenomena.
   - CPS often begin with arrest & stare; oroalimentary & complex automatisms are common.
   - posturing of contralateral arm may occur; nose wiping with ipsilateral arm is specific for MTS
   - seizure usually lasts 1-2 mins.
   - postictal disorientation, recent-memory deficit, amnesia of ictus and (in dominant hemisphere) aphasia usually last several mins.

2. Most patients have *material-specific MEMORY impairment* that lateralizes to side of seizure onset - either verbal or visuospatial skills (depending on whether epileptogenic temporal lobe is dominant or nondominant) – only finding on physical exam!

3. Patients also may have **FRONTAL LOBE dysfunction** on neuropsychological testing.

**Semiology of frontal versus temporal lobe seizures:**

<table>
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<tr>
<th>FEATURES</th>
<th>FRONTAL LOBE</th>
<th>TEMPORAL LOBE</th>
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</thead>
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<tr>
<td>Seizure frequency</td>
<td>Frequent, often daily</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Sleep activation</td>
<td>Characteristic</td>
<td>Less common</td>
</tr>
<tr>
<td>Seizure onset</td>
<td>Abrupt, explosive</td>
<td>Slower</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Slower</td>
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<td>Initial motionless staring</td>
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<td>Common</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Less common</td>
<td>More common and longer</td>
</tr>
<tr>
<td>Bipedal automatism</td>
<td>Characteristic</td>
<td>Rare</td>
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<tr>
<td>Complex postures</td>
<td>Early, frequent, and prominent</td>
<td>Late, less frequent and less prominent</td>
</tr>
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<td>Hyperkinetic motor signs</td>
<td>Common</td>
<td>Rare</td>
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<td>Somatosensory symptoms</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Speech</td>
<td>Loud vocalization (grunting, screaming, moaning)</td>
<td>Verbalization speech in non-dominant seizures</td>
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<tr>
<td>Seizure duration</td>
<td>Brief</td>
<td>Longer</td>
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<td>Secondary generalization</td>
<td>Common</td>
<td>Less common</td>
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<td>Postictal confusion</td>
<td>Less prominent or short</td>
<td>More prominent and longer</td>
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<td>Postictal dysphasia</td>
<td>Rare, unless it spreads to dominant temporal lobe</td>
<td>Common in dominant temporal lobe seizures</td>
</tr>
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**DIAGNOSIS**

**EEG**
**Interictal EEG** - *slowing and spikes* (or *sharp waves*) in **temporal region** (in 20-30% cases, discharges are bilaterally independent - do not necessarily indicate presence of bilateral epileptogenic regions).

N.B. unilateral mesial temporal lobe epilepsy often gives **bitemporal spikes** (if seizures are unilateral, then bitemporal spikes are not contraindication for surgery, although surgery outcomes are worse)

- usually maximal at **anterior** temporal (F7 and F8) and **mid** temporal regions (T3 and T4 electrodes).
- accentuated **during NREM sleep**.
- EEG yield is increased with **additional basal electrodes** (sphenoidal, inferior temporal, nasopharyngeal) or with dense-array EEG.

Epileptiform discharges focally over right temporal lobe (bottom four lines) and intermixed irregular slow-wave activity (not seen on other side):

**Ictal EEG**: *attenuation* (regionalized or generalized) → gradual buildup of rhythmical *theta* or *alpha frequencies* intermixed with *epileptic discharges*.

- EEG manifestations are maximal:
  - **mesial TLE** – in anterior or mesial temporal region.
  - **neocortical TLE** – in lateral or posterior temporal area.

Rhythmic theta activity maximal at left sphenoidal electrode during mesial temporal lobe epilepsy seizure:
IMAGING

High-resolution MRI in mesial temporal sclerosis:

N.B. radiologic findings may be extremely subtle!

1) hippocampal atrophy - more specific, but reliably detected only by thin section volumetric acquisitions in coronal plain (high-resolution T1-MRI using spoiled gradient-recall sequences with contiguous coronal slices oriented obliquely, perpendicular to long axis of temporal lobe has 85% sensitivity).
   - more sensitive measure of hippocampal atrophy is MRI measurement of hippocampus volume.
   - dilatation of adjacent temporal horn of lateral ventricle

2) increased signal on T2-MRI and decreased on T1 (indicates areas of gliosis) - easiest to detect and most reliable (ensure that brighter hippocampus is not larger because then pathology would not be hippocampal sclerosis!).

3) loss of internal structure of hippocampus

4) atrophy of the ipsilateral fornix, mammillary body and temporal lobe (esp. temporal pole).

5) 40% of patients have hippocampal malrotation - abnormally round and vertically orientated hippocampus, and a deep collateral sulcus – also present in normal individuals:
Coronal T2-MRI - high signal in right hippocampus (white arrows; compare with normal hippocampus on left, black arrows):

Coronal MRI - right-sided hippocampal sclerosis- right hippocampal formation (arrow) is atrophic compared with left and shows signal↑ (white areas):

Coronal T1-MRI from volumetric acquisition:

**Normal hippocampus** (arrows): A - body, B – head; asymmetry is due to asymmetrical position of each slice with respect to hippocampus which is essentially unavoidable and usually appears more marked in head region.

**Left hippocampal sclerosis:** C - left hippocampus is smaller (T1-MRI), D - left hippocampus is of higher signal, adjacent left temporal horn is larger than right (T2-MRI)
FLAIR (fluid attenuated inversion recovery) is superior to T2-MRI to show signal abnormalities because saturation nullifies signal from CSF:

A. T2-MRI shows volume reduction of left hippocampus.
B. FLAIR sequence shows abnormal high signal (arrow), not seen on T2 scan.

Bilateral mesial temporal sclerosis:
Source of picture: Viktoras Palys, MD
**FDG-PET** (positive in 85-90% patients with intractable TLE) - focal **hypometabolic areas much larger than epileptogenic zone** (e.g. in medial TLE, hypometabolism involves both medial and lateral temporal lobe cortex ± subtle regions of hypometabolism in frontal lobe, thalamus, basal ganglia).
- hypometabolism degree does not correlate with cell loss degree or hippocampal atrophy degree identified by MRI.
- short half-life of isotope precludes use for ictal studies (*ictal* PET would demonstrate **hypermetabolism**).

35 yo male, right temporal cortical hypometabolism, more prominent in the lateral temporal cortex compared to the medial. These changes are compatible with an interictal epileptogenic zone (anterior → posterior coronals):

- **11C-flumazenil PET** (labels central GABA receptors) - **reduction in FMZ binding** in temporal lobe (correlates with neuron loss in hippocampus*).
  - *FMZ binding is greater than what would be expected from volume loss alone (in addition to neuronal loss, GABA binding in epileptogenic hippocampus is reduced).
- may have greater localizing sensitivity than FDG-PET.

**SPECT** - *interictal* epileptogenic temporal lobe **hypoperfusion** (in > 50% patients); false lateralization occurs in 15-20% cases.
- long half-lives of isotopes make *ictal* SPECT possible (65-90% ictal SPECTs demonstrate epileptogenic temporal lobe **hyperperfusion**).
  - *HMPAO is injected during seizure and is retained in grey matter for several hours - imaging can take place postictally.

N.B. obtaining true ictal injection is important, since with late injections, areas of increased perfusion represent seizure spread rather than seizure onset.
**HMR spectroscopy**

- **reduction in NAA/(Cho + CR) ratio** in affected temporal lobe (97%).
  - NAA (N-acetyl aspartate) is found primarily within neurons and precursor cells; NAA reduction indicates loss or dysfunction of neurons.
  - CR (creatinine) and Cho (choline) are present in much higher concentrations in glia than in neurons.
  - 20-40% patients have bilateral abnormalities (higher probability of surgical failure).

**SEEG**

- indications - see p. E13 >>
- technical aspects - see p. E13 >>

**TREATMENT**


- **CARBAMAZEPINE** and **PHENYTOIN** are drugs of choice.
- newer anticonvulsants (**GABAPENTIN, LAMOTRIGINE, TOPIRAMATE**) may also be effective.
- drugs usually suppress *secondarily generalized seizures*, but 30-40% patients continue to have *partial seizures*.
- seizures often become medically refractory → proceed with surgical evaluation quickly (esp. with structural lesions in temporal lobe) - respond well to:
  - a) **open anterior temporal lobectomy**!!! see p. E15 >>
  - b) **stereotactic laser ablation.** see p. E15 >>
  - c) **stereotactic radiosurgery (SRS)** - rate of seizure freedom comparable to open resection.
N.B. therapeutic effects are delayed up to 2 years; potential for radiation necrosis.

d) **stereotactic RF ablation**
e) **neuromodulation (RNS, DBS)** - good palliative effect and reduces SUDEP; some patients become seizure free for extended periods of time but sooner or later still recur.

**Bitemporal epilepsy**
- bitemporal RNS
- resect more affected side; seizures easier controlled with AEDs

**MTS + other lesion**
- there is speculation in the literature about the relationship of these entities – it is possible that an extra-hippocampal lesion may cause seizures that spread through the hippocampus and, over time, this spread pattern could damage the hippocampus through excitotoxicity and render it an independent source of seizures.
- patients with **hippocampal atrophy and dysfunction** (temporal lobe-specific poor memory) in whom the other data are concordant for the temporal lobe undergo combined resection (lesion and hippocampus); the more medial the lesion, the more likely is the true dual pathology.
- **patients without evidence of hippocampal dysfunction** (on neuropsychological studies and WADA) undergo lesionectomy without hippocampectomy (regardless of the volume of the hippocampus, although a small proportion of these patients may need further resection).

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**EXTRATEMPORAL NEOCORTICAL EPILEPSY**
- less studied and understood than temporal epilepsy.

| According to frequency: TEMPORAL > FRONTAL > PARIETAL ≈ OCCIPITAL |

**ETIOLOGY**
- in 25% cases, no cause is identified.
- **most common etiologies** - neoplasm, head injury, CNS infection, vascular malformation, neuronal migration disorder.
  - N.B. location of epileptic focus does not predict etiology (except **HEAD TRAUMA** - commonly produces contusions of frontal & temporal polar regions and orbitofrontal cortex)

**CLINICAL FEATURES**

**FRONTAL LOBE**
- **COMPLEX PARTIAL SEIZURES** with various seizure patterns: see p. E1 >>
  a) **orbitofrontal cortex & cingulate gyrus** - staring, automatism, autonomic and affective manifestations, agitation with prominent motor activity and thrashing (“bizarre hyperactive seizures”).
  b) **supplementary motor area** - nocturnal seizures with preserved consciousness and bilateral asymmetrical tonic posturing (!), monotonous vocalizations.
  c) **opercular area** - facial clonic twitching, salivation, mastication, speech arrest, laryngeal symptoms, autonomic signs, gustatory or epigastric disturbances.
  d) **dorsolateral frontal convexity** - focal tonic and clonic activity, head-eye-body version, speech arrest.
unique characteristics: rapid seizure spread, bifrontal synchrony.
SECONDARILY GENERALIZED tonic-clonic seizures are common.
differentiate from movement disorders, parasomnias, psychogenic seizures.

**PARIETAL LOBE**
- lateralized somatosensory symptoms, vertigo, epigastric or cephalic sensations.
- anterior parietal lobe seizures may spread to frontal lobe, posterior parietal lobe seizures usually spread to temporal lobe.
- unique characteristics: auras, rare secondary generalizations.

**OCCIPITAL LOBE**
- elementary visual hallucinations (may be limited to contralateral hemifield), sensations of eye movement, forced eye blinking, postictal blindness.
- unique characteristics: auras, rare secondary generalizations.
- differentiation from migraine may be difficult (epileptic aura is brief, does not migrate across visual field; however, visual image may rotate in place; consist of colorful shapes in central visual field).

**DIAGNOSIS**

**EEG**
- may be normal when seizures arise from deep, midline, or basal locations (unless special recording techniques or montages are employed).
- nonspecific slowing, focal or bilateral epileptiform discharges, low-voltage fast activity.
- secondary bilateral synchrony (unilateral deep or midline focus produces bilaterally synchronous and symmetrical epileptiform activity) may be mistaken for generalized epileptic discharges (found in idiopathic generalized epilepsy).
- intracranial EEG monitoring is required in medically refractory cases when MRI fails to reveal focal pathology (→ tailored cortical resection).

**TREATMENT**
- lesionectomy (for structural lesions) or tailored (EEG-guided) cortical resection (for nonlesional extratemporal epilepsy)
  - surgical treatment may be limited by involvement of eloquent (motor or language) cortical regions (H: multiple subpial transections).
  - prognosis is less favorable when imaging studies fail to reveal focal abnormality.
  - frontal lobe – accounts for 20-30% of focal epilepsies but only 10-20% of all surgical cases.
  - occipital lobe – accounts for 8% of focal epilepsies.
  - parietal lobe – accounts for 1.4% of focal epilepsies.

**INSULAR EPILEPSY**

- insula has broad reciprocal connections with frontal, temporal, and posterior cortical structures → heterogeneous mix of semiologies (“the great mimicker”).
  - about detailed insular anatomy and physiology – see p. A134 >>
- according to electrocortical stimulation studies - 4 qualitatively and spatially distinct areas in the human insular cortex:
  1. General somatosensory
  2. Thermal and pain perception
  3. Viscerosensation (interoception)
  - other sensations, however, including vestibular sensations, a feeling of movement, auditory sensations, and speech impairments have also been described.
- seizures tend to feature preserved awareness.
- multiple auras:
  a) feeling breathless (patients clutch at their throat) due to pharyngolaryngeal constriction
  b) painful sensations (patient’s expression of pain)
  c) gustatory auras
  d) perioral dysesthesia of electricity or warmth
  e) rising epigastric sensation - typically attributed to onset in the insular region
  f) lateralized somatosensory sensations
- semiology variants:
  a) altered awareness and automatisms similar to temporal lobe seizures.
  b) hypermotor or tonic features similar to frontal lobe epilepsy.
  c) spasms and reflex epilepsy including audiogenic and somatosensory evoked seizures
  d) focal somatomotor signs
  e) dysarthria or dysphonic speech
Semiologic subgroups of insular-opercular seizures

- 37 patients:
  - Group 1: 4/37 Epigastric sensation and integrated gestural motor behavior or fear/rage. No facial or orofacial signs – Involves the anterior ventral insula
  - Group 2: 9/37 Auditory sensation and symmetric proximal/axial tonic sz. No focal motor or orofacial signs – posterior ventral insula
  - Group 3: 17/37 Elementary orofacial signs and laryngeal signs. Autonomic and focal motor signs. Anterior dorsal insula
  - Group 4: 7/37 Somatosensory aura → nonintegrated gestural motor behavior and/or asymmetric tonic seizures. Dorsal posterior insula

Wang et al., 2020
Diagnosis

Scalp EEG changes can be variable or misleading
Insular spikes simply may not be seen or they may be over frontopolar and frontotemporal regions (anterior insular foci) or over the midtemporal region or central leads (posterior insular foci) = false localization.
Ictal patterns seen are generally nonspecific
N.B. long latency from electrical onset and hypermotor manifestations suggests insular onset

Treatment

• for nonlesional insula plan to use RNS (laser heat may spread to white matter).
• Dr. Gonzalez-Martinez: avoid posterior insula resections - very high (13%) risk of permanent hemiparesis:
OUTCOMES
- according to studies, insular cortical resection does not affect cognitive functions.

GELASTIC SEIZURES
- pathologic bursts of laughter or giggling unaccompanied by any emotional content, i.e. no appropriate affective tone

ETIOLOGY
hypothalamic, mesial temporal, frontal cingulate.

TREATMENT
Drug-refractory cases of gelastic seizures are amenable to surgical treatment
Surgical treatment of extra-hypothalamic epilepsies presenting with gelastic seizures. Epi Disorders. Volume 21, issue 3, June 2019

BENIGN CHILDHOOD PARTIAL EPILEPSIES (BCPE)
Epilepsy Syndromes

- idiopathic localization-related epilepsies:
  
  1) with **central midtemporal spikes** (**ROLANDIC EPILEPSY**) - most common (15-20% of all childhood epilepsies!).
  
  2) with **occipital paroxysms** (**BCPEOP**)

  - 15-30% patients have family history of epilepsy; inheritance pattern, although clearly familial, is probably multifactorial and less well understood (**AUTOSOMAL DOMINANT** inheritance with age-dependent penetrance is suspected).

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**Clinical Features**

**Rolandic Epilepsy**

- occur in neurologically normal children.
- **age of onset** ranges from 2-13 years (peak at 9 years).
- brief **Simple Partial Seizures** (hemifacial sensorimotor symptoms* → may progress to hemiconvulsions → secondarily generalization to TCS → Todd's paralysis) typically **during NREM sleep** (sleep promotes secondary generalization).
  
  *e.g. gagging, drooling, anarthria, guttural noises, dysphagia, paresthesias of face, gums, tongue, and inner cheeks

- headache, nausea & vomiting occur postictally in 20-30%.
- in 80% cases, seizures are isolated or infrequent.
- prognosis is uniformly good - **spontaneous remission** in all patients by age 16-18 yrs (although 1-2% experience rare TCS in adulthood).

**BCPEOP**

- visual symptoms with frequent evolution to hemiclonic, complex partial, and TCS.
- tonic eye deviation, vomiting, consciousness alteration are also observed.
- seizure control is achieved in only 60% patients; 5% develop new seizure types in adulthood.

**Diagnosis**

- **neuroimaging** - normal.
- **interictal EEG:**
  
  **Rolandic Epilepsy** - stereotypic unilateral* or bilateral high-voltage diphasic **centrotemporal sharp waves** on normal background;  
  
  *switch from side to side on successive EEGs  
  
  - epileptiform activity is markedly enhanced **during NREM sleep**;
  
  - pattern is also seen in 15-30% first-degree relatives (but > 50% of them never have clinical attacks).

  **BCPEOP** - **occipital** (or **posterior temporal** spikes or **sharp waves**) appear with **eye closure** and attenuate with eye opening.

**Treatment**

Only ≈ 50% patients require treatment!

Isolated or rare nocturnal seizures - treatment not necessarily required.

**Frequent TCS or seizures during wakefulness** → AED treatment;

  - equally effective - **CARBAMAZEPINE** (preferred for low incidence of adverse reactions), 
  **PHENYTOIN, PHENOBARBITAL, VALPROATE**.
  
  - seizures are **easily controllable** - low doses, producing "subtherapeutic" serum concentrations, are generally effective.
  
  - **treatment termination** should be considered:
a) after 1-2 years of seizure control  
b) by age 16 years.

**EPILEPSIA PARTIALIS CONTINUA (EPC)**

- simple partial status epilepticus of motor cortex.
  
  - repeated (at intervals of few seconds or minutes) clonic or myoclonic jerks.
  - involves *one side of body* (part ÷ all).
  - *may march* from one muscle group to another (extent of motor involvement waxes and wanes in endless variation).
  - etiology:
    
    **adults** - subacute / chronic inflammatory brain diseases (e.g. Russian spring-summer encephalitis, Behçet disease), acute strokes, metastases, metabolic encephalopathies (esp. hyperosmolar nonketotic hyperglycemia).
    
    **children** - Rasmussen syndrome (s. Kozhevnikov, Kojevnikoff epilepsy).

**RASMUSSEN syndrome (s. KOZHEVNIKOV, KOJEVNIKOFF epilepsy)**

- rare childhood epilepsy syndrome with EPC.

  **etiology**
  
  - CHRONIC FOCAL ENCEPHALITIS (infectious agent has not been identified).
    
    - 66% patients report nonspecific infectious or inflammatory illness 1-6 months before EPC onset.

  **pathogenesis**
  
  - autoantibodies against GLUTAMATE receptors: receptor activation → depolarization → seizures → excitotoxic cell injury.

  **clinical features**
  
  - begins before age of 10 years.
  - generalized TCS are often first sign (appear before EPC establishes itself); 20% cases begin with convulsive status epilepticus.
  - *inevitable slow neurologic deterioration* - mental impairment, HEMIPARESIS, HEMIANOPIA, APHASIA (if affected dominant hemisphere).
  - potentially lethal, but more often becomes self-limited with significant focal neurologic deficits.
  - in some cases, seizures spontaneously remit.

  **diagnosis**
  
  - EEG - always abnormal, but non-specific (may not correlate with clinical manifestations).
  - MRI: early unilateral cortical swelling followed by cortical / subcortical FLAIR hyperintensity → progressive cortical atrophy with gliosis.
    
    - perisylvian region has been observed to be the predominant.
    
    - volume loss of the ipsilateral caudate head is frequently observed.
**TREATMENT**

- AEDs, corticosteroids, antiviral agents are usually ineffective.
- IVIG has offered short-term benefit in some patients.
- **functional hemispherectomy** can control seizures;
  - performed if seizures have not spontaneously remitted by time *hemiplegia and aphasia are complete*;
  - whether hemispherectomy should be performed *before maximal motor or language deficit* has developed is controversial.
- reports of successful RNS implantation.

**GENERALIZED EPILEPTIC SYNDROMES**

**ABSENCE EPILEPSY (AE)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>CHILDHOOD AE</th>
<th>JUVENILE AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Onset</td>
<td>age 4-8 years</td>
<td>≈ age 12 years</td>
</tr>
<tr>
<td>TCS</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>myoclonic seizures</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>absence status epilepticus</td>
<td>10-20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

- inherited (responsible gene not identified) - family history of epilepsy is present in 30%.
- normal intelligence and neurological examination.
- typical remission by early adulthood (TCS, if present, are likely to persist!).

**DIAGNOSIS**

**EEG** - **3.0 Hz spike-wave complexes** (in juvenile AE, irregular 3.5-6.0 Hz polyspike-wave complexes are commonly observed); normal background. see p. E1 >>
  - provoked by *hyperventilation* (80%), *photostimulation* (30%).

**Neuroimaging** – normal and not required (unless atypical features are present).

**TREATMENT**

**ETHOSUXIMIDE** or **VALPROATE** *monotherapy* - effective in 80%.

*drug of choice (because ETHOSUXIMIDE is not effective against TCS)

- 5-20% require **combination** (ethosuximide, valproate, benzodiazepines, acetazolamide, lamotrigine).

**JUVENILE MYOCLONIC EPILEPSY (JME)**

- one of most frequent types of idiopathic generalized epilepsy (5-10% of all epilepsies).

**ETIOLOGY**

- genetic syndrome (gene locus on 6p; gene product is not known).
50% have relatives with seizures.
30% have asymptomatic family members with generalized epileptiform abnormalities on EEG.

**Clinical Features**
- onset - 12-18 years (8-20 years).
- single or repetitive bilaterally synchronous and symmetrical MYOCLONIC JERKS of neck, shoulders, and arms;
  - consciousness preserved.
  - predominantly in *early morning hours* shortly after awakening (makes hair-combing and tooth-brushing difficult).
  - precipitated by sleep deprivation!
  - *intensity varies* from bilateral massive spasms and falls to minor isolated muscle jerks that patients consider nothing more than "morning clumsiness".
  - 90% also have TCS (start with series of jerks in rapid succession - "clonic- tonic-clonic" seizures), 33% - absences.
  - *normal intelligence, normal neurologic examination.*

**Diagnosis**

**Interictal EEG** – generalized bilaterally synchronous 4-6 Hz (POLY)SPIKE-WAVE complexes superimposed on *normal background.*
  - *photoparoxysmal response* is elicited in 30% patients.

**Ictal EEG** - bursts of generalized, synchronous, symmetrical 10-24 Hz POLYSPIKES followed by irregular slowing.
**Neuroimaging** - *normal results* (need not be routinely performed unless atypical features are present).

**TREATMENT**
- *photosensitive patients* should limit exposure to flashing lights.
- **VALPROATE** is drug of choice (effective in 85-90%).
- also effective AEDs – LAMOTRIGINE, TOPIRAMATE, benzodiazepines.
- ETHOSUXIMIDE is not effective.

**PROGNOSIS**
- seizures are *well controlled* in most patients (if precipitating factors are avoided).
- > 90% relapse after medication withdrawal - AED therapy should be maintained indefinitely even in patients with long seizure-free intervals!

**MYOCLONIC EPILEPSIES OF INFANCY AND CHILDHOOD**

**EARLY MYOCLONIC ENCEPHALOPATHY**
- affects *severely neurologically impaired infants* shortly after birth.
- erratic fragmentary myoclonus, generalized myoclonic, tonic, and focal motor seizures.
- EEG - suppression-burst pattern that evolves to hypsarrhythmia or multifocal spike discharges within months.
- AED are ineffective.
- **prognosis is poor** - 50% patients do not survive beyond first year of life!

**EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (s. OHTAHARA SYNDROME)**
- *tonic spasms* beginning in first few months of life.
- *rapid progression* from normal to severe neurological disability (congenital malformations are commonly found), frequently evolving to West’s syndrome, followed by Lennox-Gastaut's syndrome.
- EEG - suppression-burst pattern → hypsarrhythmia, slow spike-wave complexes, multifocal spikes.
- AEDs are usually ineffective.
- **prognosis is poor** - 50% patients do not survive beyond first year of life!

**BENIGN (s. TYPICAL) MYOCLONIC EPILEPSY OF INFANCY**
- *myoclonic seizures* in *neurologically normal children* in 1-2 years of life.
- history of febrile seizures is common; family history of seizures is reported in 30% cases (familial autosomal dominant form is thought to be linked to chromosome 20).
- TCS may develop in adolescence.
- interictal EEG – *normal*.
- seizures readily controlled with **VALPROATE**.
**Epilepsy Syndromes**

- **Prognosis is good** - normal development and myoclonus cessation by age 2 yrs.

**Epilepsy with Myoclonic Absences**

- Rhythmic myoclonic seizures with consciousness impairment beginning in childhood.
- Provoked by hyperventilation.
- 50% are cognitively impaired before seizure onset.
- **EEG** - 3.0 Hz spike-wave complexes.
- Often medically refractory (Valproate and Ethosuximide may be effective).

**Sodium Channel Mutations**

As of 2014, there are three voltage-gated sodium channel genes associated with severe human epilepsies, **SCN1A**, **SCN2A**, and **SCN8A**. Voltage-gated sodium channels allow for the influx of sodium into the cell upon a change of membrane potential – the ion channels are crucial for propagating the excitatory or inhibitory action of neurons along the dendrites, cell body, and axon.

Ion channels encoded by the **SCN2A**, **SCN8A**, and **KCNQ2** genes are located at the axon initial segment, the part of the neuron where all excitatory and inhibitory impulses at the neuronal membrane are integrated and translated into an action potential. Mutations in all three genes are now associated with severe epilepsies. For **SCN2A** and **SCN8A**, the mutations are assumed to be excitatory; for **KCNQ2**, the mutations are thought to be dominant negative.

![The phenotypic spectrum of SCN8A encephalopathy](image)

Ion channels at the Axon Initial Segment

**SCN8A (Nav1.6)** is located at the Axon Initial Segment (AIS)
**SCN1A** is by far the most common and best studied voltage-gated ion channel. The SCN1A channel is mainly expressed on inhibitory interneurons, and lack of SCN1A, for example due to a truncating mutation, disruptive missense mutation, or deletion leads to the phenotype of Dravet Syndrome, a severe, fever-associated epileptic encephalopathy. It is well accepted that in SCN1A-related Dravet Syndrome, lack of the sodium channel on inhibitory cells leads to decreased inhibition and net excitation. Basically, the neurons that are supposed to inhibit neuronal activity are reduced in their activity – resulting in too much excitation and epilepsy.

**SCN2A, SCN8A.** In contrast to SCN1A, SCN2A and SCN8A channels are expressed on excitatory pyramidal cells. Both ion channels are expressed at the axon initial segment (AIS). Given the pivotal location of the AIS, it serves as the neuron’s main decision making center. It is at the AIS, where all the excitatory and inhibitory signals running up and down the neuron are integrated and where the decision is made whether the neuron will fire. Accordingly, changes in channel properties at the AIS can be far-reaching. Understanding the consequences of **SCN2A** and **SCN8A** mutations involves two opposite scenarios. First, what happens if the channel is less active, either due to a particular mutation or through a truncating mutation or deletion? For both SCN2A and SCN8A, these questions have been answered. Loss-of-function mutations in SCN2A can lead to autism and intellectual disability, and loss-of-function mutations in SCN8A lead to intellectual disability and ataxia (OMIM614306). These phenotypes are completely different to the epilepsy phenotypes due to gain-of-function. For SCN2A, likely gain-of-function mutations result in epileptic encephalopathy. For SCN8A, the story was not clear for a long time. The publication by Larsen and collaborators now highlights the fact that epileptic encephalopathy is a common consequence of likely activating mutations.

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**SEVERE (s. COMPLEX) MYOCLONIC EPILEPSY IN INFANCY (SMEI), s. DRAVET syndrome (DS)**

- DS is a severe epileptic encephalopathy that is difficult to recognize at the time of onset or at any single point in time – **DS evolves over years**.

  - first described by Dravet in 1982 and was added to the International League Against Epilepsy (ILAE) classification in 1989.
  - in 2001 ILAE, DS encompasses:
    1) SMEI
    2) “borderline” SMEI (SMEB) - SMEI with less frequent seizures and atypical features.

**Epidemiology**

- DS is found in 1 per 20,000-40,000 members of population.
- male-to-female ratio = 2 to 1.
- 3-8% of patients with their first seizure before age 1 year have DS.

**Genetics**

- mutations within **SCN1A gene** - gene for a subunit of voltage-gated sodium channel.
  - most mutations occur de novo, but inherited cases and parental mosaicism are also described.
  - 20% of DS patients do not have a detectable SCN1A mutation.
- family history (epilepsy or febrile seizures) positive in 25% of cases.
**Clinical Characteristics**

1) seizures **begin in the first year of life** in all cases
2) **polymorphic seizure semiology**:
   - early seizures are typically prolonged and associated with fever or infection
   - by age 2 years, polymorphic seizure semiology emerges - may include focal and generalized myoclonus, atypical absence, complex partial (atonic, autonomic, automatisms), and “obtundation status” (fluctuating alteration of consciousness with reduced postural tone and myoclonic jerks)
   - seizure triggers include fever, infectious illness, increased body temperature (e.g., hot bath water), and photic or pattern stimulation.
3) **seizure intractability**.
4) **developmental regression**:
   - development is always normal at onset → plateau → progressive decline between 1 and 4 years of age, typically in the second year of life.
   - degree of neurobehavioral impairment is reported to range from minor learning difficulty to global developmental delay.

**Diagnosis**

**EEG** - normal at onset, but progresses to generalized spike-and-wave discharges.
- like seizure semiology, variety of interictal EEG findings is common (some patients may have persistently normal interictal records)

**Neuroimaging** - normal.

**Testing for SCN1A mutation** is commercially available.

**Differential Diagnosis**

- children with DS are frequently initially diagnosed with febrile seizures or febrile status epilepticus.
- subsequent alternating hemiconvulsions make structural lesion improbable.
TREATMENT

Intractability!

- resources for parents - the International Dravet syndrome Epilepsy Action League (www.idea-league.org).
- avoidance of triggers is very important (avoiding hot baths or using cooling vests in hot weather if hyperthermia sensitive, or wearing sunglasses if photosensitive)
- carbamazepine and lamotrigine show exacerbation of seizures!!
- VALPROATE and TOPIRAMATE are the most promising agents; LEVETIRACETAM is also used.
- STIRIPENTOL (inhibitor of cytochrome P450) is added to combination of valproate and clobazam and is particularly effective against status epilepticus.
  - FDA approved for seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- ketogenic diet is another option.
- June 25, 2018 FDA approved Epidiolex (CANNABIDIOL) [CBD] oral solution for patients ≥ 2 yo; phase 3 trial show statistically significant reduction (from 39% to 13%, p=0.01) in monthly convulsive seizures compared to placebo.
- FENFLURAMINE (FDA approved for DS) – excellent effect!!! 70% of patients taking fenfluramine, the number of seizures per month went from about 40 to one or two per month; post hoc analysis of data from NCT02682927, NCT02826863, NCT02926898: fenfluramine treatment provided significant

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**Table**

**Differential diagnosis of Dravet syndrome**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>DS</th>
<th>FS</th>
<th>SIMFE</th>
<th>BME</th>
<th>LGS</th>
<th>MAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset &lt;1 y</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Fever-sensitive seizures</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
</tr>
<tr>
<td>Hemiconvulsion</td>
<td>+</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Generalized convulsion</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
<td>−</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Tonic seizures</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Atypical absence seizures</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Generalized ED</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Multifocal ED</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Abnormal development</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal brain MRI</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

DS = Dravet syndrome; FS = febrile seizures; SIMFE = severe infantile multifocal epilepsy; BME = benign myoclonic epilepsy; LGS = Lennox–Gastaut syndrome; MAE = myoclonic astatic epilepsy; ED = epileptiform discharges; + = usually present; +/− = maybe present; − = usually absent.
seizure reductions for children, age 2-19 with Dravet syndrome, when taken with concomitant antiseizure medications.

**PROGNOSIS**

- **outcome is poor** - after 4 years of age, patients reach steady state of intractable seizures, intellectual impairment, behavioral disorders, and neurologic abnormalities; myoclonic seizures usually cease and are replaced with nocturnal generalized clonic or absence seizures.
- **mortality rate is approximately 16%** and is related to prolonged convulsive seizures, drowning, and sudden unexpected death.

**BENIGN NEONATAL CONVULSIONS**

- rare neonatal syndromes of seizures beginning in first week of life:

1. **Benign idiopathic neonatal convulsions (BINC), s. FIFTH-DAY FITS** – 2-7% of neonatal convulsions.
   - etiology and pathophysiology unknown.
   - onset – 4-6\(^{th}\) day of life.
   - recurrent focal or generalized clonic or tonic seizures, apneic events, status epilepticus.
   - *family history of epilepsy* may be present.
   - most are *neurologically normal*.
   - *spontaneous remission* within days to weeks.

2. **Benign familial neonatal convulsions (BFNC)** – only 150 cases reported in literature.
   - AUTOSOMAL DOMINANT genetic defect on 20q13.2-13.3 (*voltage-gated K\(^+\) channel*) - family history of neonatal seizures with spontaneous remission.
   - onset – 2-3\(^{rd}\) day of life.
   - minor neurological findings have been reported.
   - seizures recur for several months.
   - 11-15% patients experience (a)febrile seizures during childhood.

**DIAGNOSIS**

- diagnosis *of exclusion* and usually made *retrospectively* (after neurological deterioration and other seizure disorders failed to emerge).

- EEG – normal or:
  a) *"theta pointu alternant"* - discontinuous, unreactive theta rhythm (associated with neonatal seizures of various etiologies).
  b) focal or multifocal abnormalities.

- laboratory and neuroimaging results are unrevealing.

**THERAPY**

- AEDs have no consistent effect on duration of seizures.
- family history of BFNNC, infrequent seizures - do not require AED therapy.
CRYPTOGENIC / SYMPTOMATIC, AGE-RELATED

FEBRILE SEIZURES

- benign GENERALIZED CONVULSIONS that occur during febrile illness that does not involve brain (i.e. source of fever is outside CNS).

- genetic etiology (mode of inheritance is unknown); 25-40% patients have family history of febrile seizures.

- asymptomatic family members:
  - risk of febrile seizures 2-3 times that of general population.
  - may have generalized epileptiform activity and photosensitivity.

- poorly understood relationship between febrile seizures and mesial temporal lobe epilepsy (prolonged febrile convulsions produce ischemic changes in hippocampal neurons?).

**CLINICAL FEATURES**

- onset: 3 months ÷ 7 years (peak incidence 18-24 months).

- seizures occur during sudden temperature rise (in early course of illness – often seizure is first indication of illness);
  - 37.9°C may be enough to cause seizures.
  - fever following immunization (vaccination fever) may also trigger febrile seizure.

**Simple febrile seizures** (80-97%) - single, generalized tonic-clonic convulsions < 15 min duration, with brief postictal period.

**Complex (s. complicated) febrile seizures** (remaining %):
  a) focal seizure (± secondary generalization)
  b) > 15 min duration.
  c) occur more than once in 24-hour period.
  d) incomplete or slow return to normal neurologic status (e.g. Todd paralysis)

**DIAGNOSIS**

Diagnosis is clinical and of exclusion!

Extent of evaluation depends on clinical history and examination:

**Simple febrile seizures** – no further evaluation is necessary* – most patients have returned to baseline by time of evaluation, so evaluations (laboratory, EEG, neuroimaging) are generally unrevealing.

*except finding source for fever

**Complex febrile seizures** (esp. with focal motor manifestations) → perform:
  1) neuroimaging - to rule out structural (focal) lesions.
  2) EEG
  3) CSF analysis - if CNS infection is suspected or if age < 1 yr.
  4) CBC, glycemia, electrolytes, urinalysis, blood culture

N.B. patients presenting with first febrile seizure before 6 months or after 5 years should be thoroughly evaluated (because secondary causes are more likely)!

**TREATMENT**

- antipyretics, tepid sponge bathing.

- repetitive seizures and status epilepticus should be terminated - intravenous benzodiazepines or PHENOBARBITAL.
**PROPHYLAXIS**

A. **Chronic AED prophylaxis** - not recommended even after 2-3 isolated convulsions (high incidence of behavioral and cognitive adverse reactions + failure to reduce risk of subsequent epilepsy).
   - if chronic prophylaxis is considered at all, it should be reserved for children with complex febrile seizures who are neurologically abnormal or who have strong family history of afebrile seizures.
   - both PHENOBARBITAL and VALPROATE are effective in reducing recurrences;
   - PHENYTOIN and CARBAMAZEPINE are ineffective!

B. If parents have severe anxiety about recurrence → **intermittent oral / rectal DIAZEPAM** (0.5 mg/kg) at onset of febrile illnesses (temp > 38.1°C) ± continued q8hrs until 24 hrs after fever subsided (preferred over chronic prophylaxis)!
   - intermittent agents that terminate simple febrile seizure of less than 5 minutes' duration: rectal DIAZEPAM, intranasal / buccal MIDAZOLAM.

N.B. although antipyretics improve child comfort, they do not prevent febrile seizures!!!

**PROGNOSIS**

- febrile seizures are neither life-threatening nor damaging to brain!

- febrile seizures are not associated with, nor do they lead to, mental retardation, low IQ, poor school achievement, or behavioral problems.

- mortality is not increased in children with febrile seizures who are neurologically normal.

- 30% experience single recurrence (of these, 50% will experience multiple recurrences); risk factors for recurrence:
  1. complex febrile seizures.
  2. age < 1 year (risk of recurrence increases to 50%)
  3. family history of febrile seizures

N.B. febrile seizures are acute symptomatic (reactive) seizures, i.e. even when recurrent, do not warrant designation of epilepsy.

- 2-3%* develop afebrile seizures (epilepsy); risk is further increased in:
  1. complex febrile seizures (risk 6-13%, up to 49%) vs. simple febrile seizure (risk is 1%)
  2. abnormal neurological examinations or abnormal development
  3. family history of afebrile seizures

*slightly higher than that in general population

**AUTOIMMUNE EPILEPSIES**

Bien C. When should autoantibody testing be performed? Program and abstracts of the American Epilepsy Society Annual Meeting; December 4-8, 2015; Philadelphia, Pennsylvania. Hot Topics Symposium.

- increasingly recognized as an occult and treatable epilepsy etiology.
- autoimmune encephalitis with seizures secondary to malignancy is a well-recognized entity, but cases without malignancy have also been well documented.
- both intracellular and extracellular antibodies have been recognized.
- highest risk - women 15-45 years, particularly those with history of autoimmune disease such as lupus or rheumatoid arthritis.
- classic semiologies - facial brachial dystonic or pilomotor seizures.
- EEG - "extreme delta brushes"
- CSF - increased cellularity and oligoclonal bands.
- MRI - changes consistent with encephalitis.
- treatable - immunotherapy may control seizures when antiepileptic drugs fail.

**WEST SYNDROME (INFANTILE SPASMS)**

- age-dependent generalized epilepsy consisting of **TRIAD**:

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1. Infantile spasms</td>
<td>2. Psychomotor retardation – moderate ÷ severe in 76-95% cases; absent in ≈ 5-10% cases</td>
</tr>
<tr>
<td>3. Hypsarrhythmia (characteristic EEG pattern) – absent in ≈ 33% cases</td>
<td></td>
</tr>
</tbody>
</table>

- INCIDENCE 24-42 of 100,000 births.

**ETIOLOGY**

A. **Cryptogenic / idiopathic** (≈ 15%)

B. **Symptomatic**:

1) **tuberous sclerosis** - one of most common (≈ 25%) etiologies!
2) **congenital malformations** (≈ 30%) - midline defects, neurocutaneous disorders, neuronal migration disorders.

**Aicardi syndrome** – inherited *agenesis of corpus callosum* with refractory infantile spasms in *female* babies; other features – neuronal heterotopias, profound psychomotor retardation, coloboma of iris and retinal lacunae, vertebral abnormalities (e.g. fusion, hemivertebrae).

*lethal in males during fetal life

3) **perinatal complications** (≈ 30%) – trauma, hypoxic ischemic injury, congenital infections.
4) **other** - tumors, infections, metabolic disorders (e.g. phenylketonuria), head trauma (esp. subdural hematoma and intraventricular hemorrhage).

**Family history** (of epilepsy or febrile seizures) is present in 10-15% cases.

**PATHOPHYSIOLOGY**

- widespread cortical dysfunction.

Postulated predisposing mechanism - **increased synthesis and activity of CRH**.

- abnormal stress during early life or errant response to common stressors → growth or hyperfunction of certain CRH-containing neuronal pathways.
- in animal studies, CRH demonstrates **excitatory effects on neurons** (including those in hippocampus).
- **number of CRH receptors** reaches maximum in infant brain followed by spontaneous reduction with age (accounting for eventual spontaneous resolution of infantile spasms).
- it is thought that **pons** is involved in spasms (pons is essential for maintenance of extensor and flexor tone).

**CLINICAL FEATURES**

**INFANTILE SPASMS** - sudden, brief (few seconds), bilaterally symmetrical simultaneous **flexions** (less commonly, **extensions**) of neck, trunk, and limbs.
- initially, movements are slight - may go unnoticed (mimic colic - infants cry and draw up legs during attack).
- **classic spasm** is sudden neck and abdomen flexion with limb extension (“salaam” or “jackknife” seizure).
- **repeated** many times day.
- occur in **clusters** (10-20 movements per episode) on awakening, during drowsiness, handling, feeding, fever.
- intensity of contractions and number of muscle groups involved vary (among individuals and in same individual during repeated attacks) - **any repetitive phenomena** (e.g. head nodding, eye elevation or deviation, movement of one limb) **should suggest infantile spasms**!
- eye movements, autonomic signs, brief lapses of consciousness may be observed.

- 85% cases appear in **first year of life** (majority between 3 and 7 months).
- **neurodevelopmental abnormalities** may precede onset of spasms.
- sleep is markedly disrupted (REM sleep↓).
- **associated abnormalities** - microcephaly, blindness, deafness, ataxia, generalized hypotonicity, paralysis.
- seizures tend to diminish with age, often abating by 5 yrs.

### Diagnosis

**Interictal EEG** – grossly abnormal - **HYPARRHYTHMIA** - chaotic high-amplitude slow waves (resembling muscle artifacts) with interspersed random **multifocal epileptiform discharges** and poor interhemispheric synchrony (no organized background rhythm!):
by age 3 years, hypsarrhythmia evolves to slow spike-wave complexes or multifocal spikes and sharp waves.

**Ictal EEG**: spasm is accompanied by abrupt attenuation (electrodecremental response - generalized low-voltage fast activity).

**NEUROIMAGING**
- abnormalities (found in ≈ 60% cases) depend on etiology – generalized atrophy, white matter hyperintensities, (multi)focal lesions.

---

**TREATMENT**

A) **STEROID THERAPY** (dose and duration has not been standardized).
   a) most common treatment – **ACTH** i/m 20-80 IU/d or 150 IU/m²/d;
      - e.g. H.P. Acthar Gel (corticotropin) injection - FDA approved on October 15, 2010
      - 70-75% achieve initial seizure control (most effective when initiated within 1 month of spasm onset – importance of early diagnosis).
      - children who respond to ACTH do so within first 2 weeks!
      - ACTH treatment should be limited to no more than 4-6 weeks (if ACTH is given for ≥ 10 months, mortality exceeds 5%).
      - within 2 months of remission, 30-50% suffer relapse.
   b) **oral steroids** (e.g. **PREDNISONE** 2 mg/kg/d)

B) **OTHER DRUGS** (*VIGABATRIN*, topiramate, phenobarbital, valproate, pyridoxine, immune globulin, nitrazepam, clonazepam) – only modest efficacy.

   - CARBAMAZEPINE, OXCARBAZEPINE, and PHENYTOIN should not be used in children with tuberous sclerosis - can precipitate or aggravate infantile spasms!

C) **SURGERY** (lesionectomy, functional hemispherectomy, multilobar resection) - for focal abnormalities on MRI or PET scans.

---

**PROGNOSIS**

*Outcome is poor!* - underlying CNS disorder plays major role in neurologic outcome!

- infantile spasm and hypsarrhythmia **diminish with age** (complete resolution in 50% by 2 years and 72-99% by 5 years).
- only 5% experience spontaneous remission without neurological sequelae; **mental retardation** is observed in 50-80%.
- in ≥ 50% spasms are replaced by other epilepsies (esp. Lennox-Gastaut's syndrome, multifocal or secondarily generalized epilepsy, other forms of epilepsy during childhood).
- 5-20% cases lead to **death**.

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**LENNOX-GASTAUT SYNDROME**

- heterogeneous group of **early childhood epileptic encephalopathies** (i.e. nonspecific brain response to diffuse neural injury).
- onset 1-8 years (peak incidence 3-5 years).

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**ETIOLOGY**

- 70% cases occur in children with **acquired / genetic CNS disorders** - congenital malformations, hypoxic-ischemic encephalopathy, CNS infections, neurocutaneous disorders (esp. tuberous sclerosis).
25-30% patients have infantile history of West's syndrome.

*family history of epilepsy* may be found in cryptogenic cases (N.B. familial Lennox-Gastaut syndrome has not been reported).

**Clinical Features**

1. **Multiple Seizure Types** (generalized atonic*, tonic, myoclonic-astatic, tonic-clonic, atypical absence)
   - *tonic seizures* (during sleep or on awakening) occur in all cases.
   - up to 50 seizures per day.
   - ≈ 66% patients experience *status epilepticus* (repetitive tonic seizures, clouding of consciousness lasting hours to weeks).

2. **Diffuse Cognitive Dysfunction**
   - in 20-60% cases, mental retardation precedes onset of seizures.
   - 50% patients have *severe mental retardation*
   - disturbances of behavior and personality are common.

**Diagnosis**

**Interictal EEG** – irregular generalized SLOW (1.0-2.5 Hz) SPIKE-WAVE COMPLEXES;
   - superimposed on *abnormal slow background activity*.
   - *during sleep* - runs of generalized paroxysmal fast activity and rhythmical 10 Hz spikes.

**Ictal EEG:**
- *tonic seizures* - electrodecremental response or generalized 10-25 Hz spikes.
- *atypical AS* - runs of slow spike-wave complexes.

**Neuroimaging** - generalized cerebral atrophy, (multi)focal abnormalities.

**Treatment**

Seizures respond very poorly to AED - *polytherapy is usually required!*

- minimize sedation (tendency for seizures to increase in sleep).
- most effective agents – CLOBAZAM (FDA approved as adjunctive treatment – best result of all AEDs), VALPROATE, LAMOTRIGINE*, TOPIRAMATE*, FELBAMATE*, CLONAZEPAM*, RUFINAMIDE* (as adjunctive treatment)
  - continued seizures (incl. dangerous drop attacks) remain common - majority of patients will have seizures throughout childhood and into their adult years.
  - CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL can provoke frequent astatic and/or atypical absence seizures!
  - benzodiazepines may precipitate tonic status!
- refractory cases may benefit from *ketogenic diet* or *surgery* - treatment of choice is *vagal nerve stimulator*; in refractory cases - corpus callosotomy (reduces drop attacks).

**Prognosis**

*Prognosis is poor!*

- *daily seizures* occur in most patients.
- 80% cases *persist into adulthood.*
• fatal injuries related to seizures occur in 5% cases.

SPECIAL EPILEPSY SYNDROMES

PROGRESSIVE MYOCLONIC EPILEPSIES (PME)

- group of disorders of various etiology.
- 1% of all epilepsies.
- typical onset - childhood or adolescence (some disorders may appear at any age).
- progressive myoclonus, seizures (most commonly TCS), variable degrees of cognitive impairment, and other neurological deficits (ataxia, spasticity, visual impairment, hearing loss, peripheral neuropathy, extrapyramidal signs)
  - myoclonus varies from mild to debilitating.
  - dementia is characteristic sign (but not universal feature).
- natural history varies from mild neurological impairment to severe disability progressing to death in early childhood; in general, prognosis is grave!
  Early PME (before severe neurological disabilities develop) may be mistaken for JME!

TREATMENT

• myoclonus responds best to VALPROATE and CLONAZEPAM.
• useful adjuncts - LAMOTRIGINE, TOPIRAMATE, FELBAMATE, Zonisamide, ACETAZOLAMIDE, ketogenic diet, L-Trp, 5-hydroxyTrp + carbidopa, PIRACETAM.
  N.B. phenytoin and carbamazepine typically exacerbate ataxia and myoclonus!
• mechanical techniques lessen incapacitating effects of action myoclonus.

CLASSIFICATION

I. Disorders with well-defined BIOCHEMICAL DEFECTS:
  1. Sialidoses (type I, type II)
  2. Sphingolipidoses (Gaucher type III, GM2 gangliosidosis)
  3. MERRF (myoclonic epilepsy with ragged red fibers)

II. Disorders with BIOLOGICAL or PATHOLOGICAL MARKERS (but poorly defined mechanism):
  1. Neuronal ceroid lipofuscinosis (late infantile, juvenile, adult)
  2. Lafora disease see below >>
  3. Other rare PMEs - childhood form of Huntington chorea, juvenile neuroaxonal dystrophy, action myoclonus-renal insufficiency syndrome.

III. DEGENERATIVE disorders (no known pathological or biochemical markers):
  1. Unverricht-Lundborg disease (s. Baltic myoclonus) see below >>
  2. Dentatorubropallidoluysian atrophy

LAFORA DISEASE (s. FAMILIAL MYOCLONIC EPILEPSY)

- rapidly progressive autosomal recessive disorder:
1. **Seizures:** *generalized TCS* or *occipital partial seizures* are usually initial manifestation → severe resting and action *myoclonus*.
2. Universal progressive *cognitive decline*.
3. **Other neurologic abnormalities** - ataxia, decreased vision, spasticity.

- **pathology** (in brain, liver, muscle, duct cells of eccrine sweat glands) – *Lafora bodies* (basophilic PAS-positive polyglucosan cytoplasmic inclusions):
  - onset – 6-19 yrs.
  - **death** within 2-10 years of onset.
  - **diagnosis:**
    1) skin biopsy.
    2) EEG - polyspike-wave discharges (particularly in occipital region) with progressive slowing and disorganized background.
  - **Valproate** and **Clonazepam** are effective.

**UNVERRICHT-LUNDBORG DISEASE (s. BALTIC MYOCLONUS)**

- occurs predominantly in Finland, Estonia, and Sweden.
- **Autosomal recessive**, 21q22.3 - gene for *cystatin B* (ubiquitous lysosomal enzyme, inhibitor of cysteine protease).
- onset – 6-15 years in individuals with no prior neurological abnormalities.
  1. Severe morning *myoclonus* (can be precipitated by movement, stress, light, noise, or tactile stimulation); may culminate in generalized *TCS* later in day.
  2. **Ataxia, intention tremor, dysarthria** usually develop in later stages.
  3. Gradual *intellectual decline* (severe dementia does not occur).
  4. Depression is common.
- **death** within ≈ 14 years of onset.
ACQUIRED EPILEPTIC APHASIA (LANDAU-KLEFFNER SYNDROME)

1) ACQUIRED APHASIA (interruption of subcortical fibers → deafferentation of language cortex → auditory verbal agnosia and spontaneous speech reduction)
   - begins before age 6 years (typically, after initial acquisition of verbal language in previously normal child).
   - language regression may be sudden; children often become mute and unresponsive to verbal commands – many are misdiagnosed as deaf or autistic.

2) EPILEPTIFORM ACTIVITY (high-amplitude multifocal spikes on normal background) over TEMPORO-PARIETO-OCcipital regions.
   - EEG abnormalities are markedly accentuated during NREM sleep.
   - 75% patients experience infrequent seizures (tonic-clonic, focal motor, atonic).

3) PSYCHOMOTOR & BEHAVIORAL difficulties (in 70% patients).
   - only 200 cases are reported in literature.
   - boys : girls = 2 : 1
   - no etiological factors have been identified.
   - no specific abnormalities in brain biopsies.
   - hearing is normal - audiometry, auditory evoked potentials, and neuroimaging results are normal.
   - spontaneous remission of seizures and EEG by age 15 years (but most will have significant speech abnormality during adulthood); some experience reoccurrence of aphasia and seizures following apparent recovery.
   - onset at age < 2 yrs - uniformly poor prognosis!

TREATMENT

- initiate speech therapy for several years.
- intravenous DIAZEPAM → dramatic (but transient) improvement in language and EEG.
- VALPROATE is anticonvulsant of choice (some children require combination with CLOBAZAM).
- benefit of long-term AED therapy has not been demonstrated!
- if seizures and aphasia persist → trial of steroids.
- when medical management fails → consider operative multiple subpial transection technique – patients may recover language!

NEONATAL SEIZURES

- most common sign of neurologic dysfunction in neonate!
- INCIDENCE unknown (= 0.3-0.6%) - lack of consensus on which behaviors constitute epileptic seizures.
- incomplete CNS myelination, incomplete arborization of axons & dendritic processes prevents synchronous and symmetrical propagation - generalized TCS are not observed in neonatal period! (neonatal seizures are fragmentary and not well sustained).
- neonatal seizures may be subtle and difficult to recognize clinically!!! (video-EEG recording may be necessary for diagnosis).

Five seizure types in newborns (usually focal):

1. FOCAL SEIZURES
2. MULTIFOCAL CLONIC SEIZURES
3. **TONIC SEIZURES** – rigid posturing of extremities and trunk ± fixed deviation of eyes.
4. **MYOCLONIC SEIZURES** – tend to involve distal muscle groups.
5. **SUBTLE SEIZURES** (most common form!!) – motor automatisms commonly observed in premature infants - are *not clearly epileptic* (do not show evidence of electrical-cortical genesis on video/EEG studies) - attributed to brain stem or frontal release phenomena: oral-buccal-lingual movements, eye movements (blinking, nystagmus), bicycling or pedaling, swimming; accompanying **autonomic phenomena** (excessive salivation, changes in color, BP changes, alterations in respiratory rate up to apnea) are common.

N.B. in preterm infants, *isolated autonomic phenomena* may be only evidence of seizure activity!

**Differentiate** from **nonepileptic phenomena** (tremor, clonus, decerebration, jitteriness) - common in diffuse cerebral dysfunction; 3 main distinguishing features:

1. *autonomic changes* (tachycardia, BP elevation, etc) do not occur with nonepileptic events (vs. common with seizures).
2. nonepileptic phenomena are *enhanced* by sensory stimuli or limb repositioning (vs. no influence on seizures).
3. nonepileptic movements are *suppressed* by gentle physical restraint (vs. true seizures are not).

**ETIOLOGY**

Neonatal seizures are *only rarely idiopathic*!

Neonatal seizures should always be considered *symptomatic* of serious underlying neurologic or systemic disease.

Metabolic, toxic, structural, infectious diseases are more likely to become manifest during neonatal time than at any other period of life - *seizures are common* manifestation of cerebral dysfunction in first 4 weeks of life!

<table>
<thead>
<tr>
<th>Causes</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia-ischemia</td>
<td>65%</td>
</tr>
<tr>
<td>Infection</td>
<td>10%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>10%</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>5%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5%</td>
</tr>
<tr>
<td>Hypocalcemia &lt; 1.7 mmol/L</td>
<td>2%</td>
</tr>
<tr>
<td>Brain malformations</td>
<td>2%</td>
</tr>
<tr>
<td>Familial</td>
<td>1%</td>
</tr>
</tbody>
</table>

**ETIOLOGIES BY PEAK TIME OF ONSET:**
<table>
<thead>
<tr>
<th>Disorder</th>
<th>24 hours</th>
<th>24-72 hours</th>
<th>3-7 days</th>
<th>7-28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrovascular</strong></td>
<td><strong>Hypoxic-ischemic encephalopathy</strong>&lt;br&gt;SAH Intraventricular hemorrhage</td>
<td>Intraventricular hemorrhage&lt;br&gt;Cerebral infarction&lt;br&gt;Intracerebral, subdural hemorrhage&lt;br&gt;SAH</td>
<td>Cerebral infarction&lt;br&gt;Intracerebral hemorrhage</td>
<td></td>
</tr>
<tr>
<td><strong>Traumatic</strong></td>
<td>Laceration of tentorium or falx</td>
<td>Cerebral contusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Bacterial meningitis&lt;br&gt;Sepsis&lt;br&gt;Intrauterine infection</td>
<td>Bacterial meningitis&lt;br&gt;Sepsis</td>
<td></td>
<td>Herpes simplex encephalitis</td>
</tr>
<tr>
<td><strong>Iatrogenic</strong></td>
<td>Anesthetic toxicity</td>
<td>Drug withdrawal: barbiturates (!!!), benzodiazepines, heroin, methadone, alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Congenital malformations&lt;br&gt;Neurocutaneous disorders</td>
<td>Congenital malformations&lt;br&gt;Neurocutaneous disorders</td>
<td>Congenital malformations</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Pyridoxine dependency&lt;br&gt;Hypoglycemia&lt;br&gt;Cocaine exposure</td>
<td>Pyridoxine dependency&lt;br&gt;Hypoglycemia&lt;br&gt;Hypoparathyroidism&lt;br&gt;Hypocalcemia&lt;br&gt;Hypomagnesemia (&lt;4.0 mmol/L)&lt;br&gt;Glycine encephalopathy&lt;br&gt;Glycogen synthase deficiency&lt;br&gt;Urea cycle disorders&lt;br&gt;Nonketotic hyperglycinemia</td>
<td>Hypocalcemia&lt;br&gt;Hypoparathyroidism&lt;br&gt;Kernicterus&lt;br&gt;Ketotic hyperglycinemia&lt;br&gt;Urea cycle disorders</td>
<td>Adrenoleukodystrophy&lt;br&gt;Fructose dysmetabolism&lt;br&gt;Gaucher disease type II&lt;br&gt;GM1 gangliosidosis&lt;br&gt;Ketotic hyperglycinemia&lt;br&gt;Maple syrup urine disease&lt;br&gt;Urea cycle disorders</td>
</tr>
</tbody>
</table>

- **hypoxic-ischemic encephalopathy** is most common etiology encountered within first 24 hours (and of neonatal seizures overall)!
- causes of **hypoglycemia** – diabetic mother, small-for-gestational-age newborn, hypoxia-ischemia or other stress. see p. 2750 >>
- unintentional **injection of local anesthetic** into fetus during labor can produce intense tonic seizures, respiratory depression; serum [anesthetic]↑ confirms diagnosis. H: promote urine output by IV fluids.

**Diagnosis**

**EEG**
- neonatal seizures may not have EEG correlate! (esp. generalized tonic, (multi)focal myoclonic, subtle seizures)
• *background abnormalities* correlate with extent of *neurological impairment* (suppressed, undifferentiated, suppression-burst patterns have high incidence of neurological and developmental sequelae).

• *isolated sharp waves* are commonly seen in *neurologically normal neonates* without seizures and are not predictive of seizures or future development of epilepsy.

• *ictal patterns* are more variable in neonates (typically - runs of focal paroxysmal activity of varying frequency and polarity).

**EEG classification of neonatal seizures**

A) *clinical seizures with consistent EEG event* - focal clonic, focal tonic, some myoclonic seizures; clearly *epileptic* - likely to respond to anticonvulsant.

B) *clinical seizures with inconsistent EEG events* - all generalized tonic seizures, subtle seizures, some myoclonic seizures; likely to be *nonepileptic* (i.e. subcortical or brain stem release phenomena rather than cortical events) - may not require or respond to antiepileptics.

C) *electrical seizures with absent clinical seizures*:
- marked by abnormal EEG background in comatose infant who is not on anticonvulsants.
- persisting electrical seizures in patients with anticonvulsant.

**Neuroimaging** (cranial ultrasound, CT, MRI) - for suspected *structural lesions*.

• investigate first with *ultrasound* (to exclude major malformations affecting midline or other types of pathology associated with ventriculomegaly).

• *CT* could wait until at least 6 (preferably 12) months of age - to give abnormal calcification time to develop.
  - negative *CT* at 3 months does not exclude tuberous sclerosis, common cause of infantile spasms.

• normal ultrasound + normal CT = most major malformations and acquired lesions are excluded → *MRI* (wait until brain is fully mature at ≈ 18 months) - to assess detailed cortical anatomy.
  
  N.B. many minor malformations (that are important causes of epilepsy) cannot be excluded until brain is fully matured!!!

**CSF analysis** - for suspected *infection* (virtually indicated in all neonates with seizures, unless cause is obviously metabolic).

**Metabolic screens** - for suspected *electrolyte disorders & inborn errors of metabolism*.

  Many inborn errors of metabolism cause generalized convulsions in newborns!

  Always rule out *hypoglycemia*!

  Always do *urine toxicologic screen* (e.g. passive cocaine intoxication may be cause!)

**Funduscropy** - for suspected *chorioretinitis (congenital infection)* → TORCH titers of mother and infant.

**TREATMENT**

• seizures generally are self-limited and rarely compromise vital function (except seizures presenting as apnea) - it is unnecessary to stop seizures in progress.

• *clinical seizures unaccompanied by EEG changes should not be treated with AED!* (AEDs are not likely to reduce clinical manifestations + high incidence of adverse reactions)

• AED is recommended for *recurrent clinical events accompanied by EEG seizure patterns*. N.B. EEG seizure activity often continues after clinical seizures stop!

**Drugs:**

• *PHENOBARBITAL* is most widely used agent; 20 mg/kg IV over 15-20 min; if seizures persist → additional 5-mg/kg increments q20min (up to total 40 mg/kg) → oral maintenance 3-7 mg/kg/d.
• alternatives (or adjuncts) – **PHENYTOIN** (only IV; poor oral absorption), **BENZODIAZEPINES**, paraldehyde (IV).

  N.B. monitor **total & free drug levels** (protein binding is altered in sick infants)

• seizures **refractory to conventional agents** → **PYRIDOXINE** 50-100 mg IV with simultaneous EEG.

Duration of AED therapy:

  a) no CNS pathology + no significant EEG abnormalities - stop AED before hospital discharge.

  b) abnormal neurological examinations, focal cerebral pathology (high risk of recurrence) - treat for longer periods (e.g. 1-3 months after last seizure), letting infant self-taper by not increasing dose with weight gain.

**PROGNOSIS**

<table>
<thead>
<tr>
<th>Severity of background EEG abnormalities* - most reliable outcome predictor.</th>
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</table>

*suppression-burst background, unreactive low-voltage recording, continuous multifocal ictal events reliably predict fatal outcome or disabling brain damage more than 90% of time!

In general, **prognosis is poor**!

**Mortality rate** for neonates with seizures:

  17-40% - for full-term infants.

  50% - for premature infants.

**Subsequent epilepsy** develops in 15-30% patients.

**BREATH-HOLDING SPELLS**

• first written description – Nicholas Culpepper (17th century English herbalist).

• various names in literature – cyanotic / pallid infantile syncope, anoxic convulsions, reflexic anoxic seizures, nonepileptic vagal attacks, white reflex syncope.

**EPIDEMIOLOGY**

• ≈ 4-5% otherwise healthy children.

• 20-30% patients have **family member** who had breath-holding episodes as child.

**PATHOPHYSIOLOGY**

- dysregulation of centrally mediated autonomic function:

  **PALLID BREATH-HOLDING SPELL** – vagally mediated bradycardia or asystole (i.e. pallid spells are actually vasovagal episodes).

  **CYANOTIC BREATH-HOLDING SPELL** (more common type) – SaO₂↓ during apneic period.

**CLINICAL FEATURES**

• first attack at 6-18 months of age (rare prior to 6 months; not later than 2 yrs).

• spells are **reflexive** **(involuntary)** - initiated by **emotional angry / frightening episode that leads to crying!!**

  – **CYANOTIC** spells often occur as part of **temper tantrum**.

  – **PALLID** spells may be provoked by **painful experience** (such as falling and striking head) or **sudden startle**.

• onset - child cries out → active full **expiration** → **apnea**:
child becomes quiet.
- mouth wide open in full expiration.
- face and trunk change color (rapid cyanosis or pallor).

- immediate further progress:
  a) **SIMPLE spell** - labored inspiration and return to normal breathing.
  b) **COMPLEX spell** - deepening of cyanosis or pallor → *loss of consciousness* (cerebral anoxia – SaO₂ decreases from 98% to 30%); *limp* muscle tone → *opisthotonus* → short generalized *clonic jerking* ± urinary incontinence (anoxic seizures) → inspiratory gasp → normal breathing; may remain motionless and hypotonic for few minutes.

  N.B. cyanosis precedes changes in muscle tone (vs. epileptic seizures - muscle activity → cyanosis).

- average attack lasts ≈ 40 seconds.
- spells are always **stereotyped**!

**DIAGNOSIS**

1. **Ocular compression test** (test of vagal stimulation) - 10 seconds of bilateral ocular compression; positive result (in 61-78% of PALLID spells and 25-33% of CYANOTIC spells):
   a) prompt and sustained bradycardia ≤ 50% of resting heart rate.
   b) asystole for ≥ 2 seconds.
   c) precipitation of clinical attack.

2. **Ictal EEG** - burst of slow waves → waves increase in amplitude → normal activity.

3. **Interictal EEG** – normal.

**TREATMENT**

- during *attack* - place in *lateral supine position* (to protect against aspiration), *keep airway patent*.
  - spell may be interrupted by placing *cold rag on child's face* at onset.
- condition is generally benign but frightening for parents - provide reassurance to parents once diagnosis has been made (parents' desire not to precipitate episode may cause them to acquiesce to all child's demands) - parents should be advised that calm, confident firmness should be used when disciplining child.

  N.B. treatment should be **BEHAVIORAL MODIFICATION** - do not reinforce child's behavior! (child cannot be given free reign of house just because spell occurred with temper tantrum; distracting child and avoiding situations that lead to tantrums are good strategies).

- anticonvulsants are not helpful!
- oral *ATROPINE* sulfate 0.01 mg/kg/24 hr in divided doses (max 0.4 mg/d) can prevent severe PALLID spells; alternative – ½ patch of transdermal *SCOPOLAMINE* every 3 days.

**PROGNOSIS**

Excellent prognosis - *spontaneous remission* at 7-8 yrs (50% - by age 4 yrs).
- 17% develop syncope following emotional provocation as adolescents or adults.

  N.B. rare cases of fatalities or brain anoxia because of prolonged apnea or aspiration!

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**CATAMENIAL EPILEPSY**

- seizure frequency↑↑↑ around time of MENSES:
  1) *estrogen & progesterone effects* on neuronal excitability
2) *altered protein binding* (changes in AED levels).

**TREATMENT**

1. **ACETAZOLAMIDE** (250-500 mg/d) as adjunctive therapy - start 7-10 days prior to menses and continue until bleeding stops.
2. **Increase AED dosage** around time of menses.
3. Control menstrual cycle with **oral contraceptives**.

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**POST-TRAUMATIC SEIZURES**

**IMPACT SEIZURES**

- generalized convulsions *at time or immediately after injury* – *acute brain reaction to trauma*;
  - more common in children than in adults.
  - *no prognostic significance* (do not increase risk of later epilepsy!)

**EARLY POST-TRAUMATIC SEIZURES**

(*within first week* following injury) – result from *acute effects of injury*

- imaging studies should be performed urgently to exclude expanding surgical lesion!!!
- rarely persist, but increase risk of developing post-traumatic epilepsy (esp. for adults).
- early PTS have not been associated with worse outcomes!

**PROPHYLAXIS**

**Indications:**
- patients at high risk:
  1. **SEVERE TBI** (GCS ≤ 10), esp. chemically paralyzed patient - obscured clinical manifestations of generalized seizures (consider continuous EEG monitoring, esp. if temporal cortex is injured)
     - 30% incidence in severe head injury, 1% in mild to moderate injuries.
     - 2.6% incidence in children < 15 yrs age with TBI causing at least brief LOC or amnesia. N.B. incidence is higher in children (vs. for late seizures)
  2. **cortical injury** - acute subdural or intracerebral hematoma, contusions, lacerations (incl. penetrating TBI), significant SAH
  3. **depressed skull fracture** with **parenchymal injury**
  4. **early** seizures (esp. seizures *within 24 hours* of injury)
  5. **intubated** patient (clinical seizures are obscured in paralyzed patients)
  6. prior **history** of seizures
  7. history of significant **alcohol** abuse

**Regimen:**

a) **(FOS)PHENYTOIN** (15-20 mg/kg loading → 5 mg/kg/24 hr divided q12hr maintenance) – drug of choice – does not alter level of consciousness!!!

*Phenytoin vs. placebo* (class I evidence) – treatment for 12 months:
### Epilepsy syndromes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Phenytoin group</th>
<th>Placebo group</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early seizure rate (cumulative)</td>
<td>3.6 ± 1.3%</td>
<td>14.2 ± 2.6%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Late seizure rate (2 years)</td>
<td>27.5 ± 4.0%</td>
<td>21.1 ± 3.7%</td>
<td>None</td>
</tr>
</tbody>
</table>


b) **Levetiracetam**: available comparative studies are insufficient to support a recommendation for or against the use of levetiracetam over another agent but it became AED of choice in TBI.

c) **Carbamazepine**

d) **Valproate** – contraindicated – interferes with platelet function, trend to worsen outcome (Dikmen et al. 2000)

- AEDs decrease frequency of seizures by 25-73%
- Anticonvulsant drug prophylactically is administered only for 7 days
  - Antiepileptics do not prevent LATE post-traumatic seizures (no need to administer for > 7 days) + possible cognitive adverse effects.
- Indications to continue past 7 days:
  1. Prior seizure history
  2. Penetrating brain injury?
  3. Patients undergoing craniotomy (surgery resets “7 days” clock)
  4. *If patient has developed seizures after first 24 hours*, antiepileptic is continued for 6 months ÷ 1 year
     - N.B. seizures within first 24 hours is not indication to extend AED beyond 7 days.
     - Remission rate ≈ 50%.
- If patient is *actively seizing* → benzodiazepines are effective rapidly acting anticonvulsants (e.g. diazepam, lorazepam), then escalate per status epilepticus protocol.

### Late Post-Traumatic Seizures

(start *after 1 week*; most commonly after 6-18 months) - *Posttraumatic sequelae.*

N.B. only recurrent late (> 7 days after trauma) seizures are called **Post-Traumatic Epilepsy**.

Seizures rise cerebral blood flow up to 400% → ICP increase → secondary brain injury.

Mechanisms of trauma-induced seizures - mechanical shearing of fiber tracts (loss of inhibitory interneurons), release of aspartate and glutamate, elaboration of nerve growth factors, reactive gliosis.

### Post-Traumatic Epilepsy

**Epidemiology**

Incidence (within 1 year) - 2.5-40% (i.e. at least 3-12 times that of general population):

1. ≈ 7% civilian head injuries
2. ≈ 34% military head injuries (higher proportion of penetrating wounds).
TBI is most common cause of symptomatic epilepsy in teenagers and young adults!

**4541 people** who suffered TBI over a 50-year period (1935–1984) in Olmsted County, MN, USA:

<table>
<thead>
<tr>
<th>Severity of TBI</th>
<th>Cumulative 5-year probability of seizure</th>
<th>Standardized incidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0.7%</td>
<td>1.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.2%</td>
<td>2.9</td>
</tr>
<tr>
<td>Severe</td>
<td>10.0%</td>
<td>17.0</td>
</tr>
</tbody>
</table>

- mild TBI - no increased risk of seizures for after 5 years.
- moderate TBI - significantly increased risk of seizures for over 10 years.
- severe TBI - significantly increased risk of seizures for over 20 years.
- strongest risk factors: brain contusions and SDH (other risk factors: skull fracture and prolonged loss of consciousness).


**78,572 people** with TBI born over a 25-year period (1977–2002) in Denmark:

<table>
<thead>
<tr>
<th>Relative risk of epilepsy after head injury</th>
<th>Relative risk of epilepsy &gt; 10 years after head injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild head injury</td>
<td>2.22</td>
</tr>
<tr>
<td>Moderate head injury</td>
<td>7.40</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>2.17</td>
</tr>
</tbody>
</table>


**RISK FACTORS**

Main risk factor - severity of head injury:

**Mild head injury** (amnesia or loss of consciousness for < ½ h, no skull fracture, no focal neurologic signs, no contusion or hematoma) does not increase risk of seizures.

N.B. rare examples of chronic epilepsy resulting from mild head injury are known!

**Severe head injury** (unconsciousness or amnesia for > 24 hours, brain contusion, intracerebral or extra-axial hematoma, persistent neurologic abnormalities [e.g. aphasia, hemiparesis, dementia]).

Other risk factors:

1) early post-traumatic seizures (24-50% risk in adults, 7-17% in children; i.e. questionable risk factor for kids)
2) repeated head injuries
3) temporal / frontal contusions
4) dura penetration increases incidence from 7-39% (with intact dura) to 20-57%.
5) cortex laceration with formation of cerebromeningeal scar (50% risk of post-traumatic epilepsy).

N.B. no evidence that deeply situated foreign body predisposes to development of seizures.

6) depressed skull fractures may or may not be risk factor (increase risk 0-17%).
7) intracranial bleeds, esp. SDH (14-35% risk in adults)
   - breakdown of hemoglobin releases iron → increased intracellular calcium oscillation and free radical formation.
8) total volume of brain lost (as measured by CT).
9) older age
10) female sex
11) focal EEG findings
12) chronic alcoholism

**Clinical Features**
- **onset:** 60% first attacks occur during first year after injury (90% within 2 years; > 15% attacks do not occur until ≥ 5 years later), i.e. seizures can start any time after TBI.
- seizures may be of **ANY TYPE** (except **classic absence**).
- more often **generalized** than focal.
- 70% patients have partial or secondarily generalized seizures.

**Diagnosis**
- epileptiform activity is seen in only 50% EEGs (H: videoEEG).

**Treatment**
- according to general principles (**benzodiazepines** are rapidly effective; **PHENYTOIN** is preferable for maintenance).
- seizures from localized **glial scars** may be unresponsive to anticonvulsants and require surgical extirpation!
- EEG to rule-out presence of seizure focus before discontinuing AEDs.

**Prophylaxis**
- **if early seizures have not occurred,** do not continue AEDs beyond initial **1-2 weeks** (no studies found protective effect beyond first week*) - adverse cognitive effects when given long-term!
  *Schierhout and Roberts 2001, Temkin 1990

**Ethanol Withdrawal Seizures (“Rum Fits”)**
- classically seen in up to **33% of habituated drinkers within 7-30 hours of cessation** or reduction of ethanol intake.
- typically 1-6 GTC seizures without focality within 6 hour period.
- seizures usually occur **before delirium** develops.
- may also occur during intoxication (without withdrawal).
- **seizure risk persists for 48 hrs** (risk of delirium continues beyond that) - single loading dose of **PHENYTOIN** is frequently adequate for prophylaxis.
  N.B. most EtOH withdrawal seizures are single, brief, and self-limited – AED prophylaxis is usually not indicated.
- **benzodiazepines** administered during detoxification reduce risk of withdrawal seizures

The following patients need head CT and should be admitted for observation:
1. First EtOH withdrawal seizure
2. Focal findings
3. > 6 seizures in 6 hrs
4. Evidence of trauma

**TREATMENT**

- seizure that continues beyond 3-4 minutes may be treated with DIAZEPAM or LORAZEPAM, with further measures used as in status epilepticus if seizures persist.
- long-term treatment is indicated:
  1. History of previous alcohol withdrawal seizures
  2. History of a prior seizure disorder unrelated to alcohol
  3. Recurrent seizures after admission
  4. Other risk factors for seizure (e.g. subdural hematoma)

**TUMOR-RELATED EPILEPSY**

Perioperative Multimodal Evaluation and Surgical Tactics of Tumor-Related Epilepsy: 2-Dimensional Operative Video >>

**Psychogenic Non-Epileptic Seizures (PNES) s. Dissociative Seizures, Pseudoseizures, Non-Epileptic Attack Disorder**

- involuntary ictal events that do not result from abnormal CNS electrical activity.
- as disabling as true epileptic seizures.

**Epidemiology**

- account for 15-30% admissions into epilepsy-monitoring units.
- women : men = 3.5 : 1.
- infrequent before 12 years (but have been observed in children as young as 4 years).
- peak INCIDENCE – 20-29 yrs.

**Etiology**

- occur in patients with: conversion disorders, anxiety and panic disorder, depression, post-traumatic stress disorder, schizophrenia, personality disorders.
- represent *subconsciously mediated behavior resulting from emotional distress* (conversion symptom).

  N.B. unlike malingerers, patients do not feign illness for obvious secondary gain!
  Patients are not deliberately attempting to mislead examining physician!

**Clinical Features**
• episodes involve **AFFECTIVE-BEHAVIORAL, AUTONOMIC, or SENSORIMOTOR** manifestations (incl. alterations in consciousness); e.g. palpitations, choking sensations, dizziness, malaise, acral paresthesias, sensory disturbances, crying.

• *micturition, injuries, amnesia, postictal somnolence* may occur.

• occur always in waking, even when patient appears asleep.

**Most distinguishing feature of true epileptic seizures is STEREOTYPY!**

"Even in the most experienced hands, a reliable diagnosis of psychogenic nonepileptic seizures by history alone is almost impossible, especially if the description of the nonepileptic event fits perfectly that of an epileptic seizure."

**DIAGNOSIS**

Diagnosis is suggested (no feature alone is definitive!):

1. personal / family history of psychiatric disease.
2. history of childhood sexual or physical abuse (present in > 66% cases)
3. atypical attacks with consistent emotional / psychologic precipitating factors
4. provoked with stimuli that would not cause seizure (e.g. tuning fork to head, alcohol pad to neck, IV saline)
5. occurrence only in presence of other persons
6. gradual onset (over minutes) and varying initial focal manifestations, nonphysiologic progression, intermittent arrhythmic and out-of-phase activity
7. prolonged seizure activity ("pseudostatus epilepticus") > 5 mins.
8. forced eye closing, resistance to eye opening, normal pupils (vs. usual pupillary dilatation that accompanies true seizures).
9. cyanosis is unusual (but breath holding may occur).
10. some patients can be persuaded to have attack on request by physician (suggestion).
11. abnormal activity stops on command or distraction (patients may communicate voluntarily during pseudoseizure).
12. absence of postictal labored breathing, drooling, confusion, and lethargy after generalized convulsion
   1) recall of ictal event
   2) repeatedly normal interictal EEGs
   3) frequent and medically refractory seizures despite therapeutic AEDs.
   4) multiple different-physician visits

• behaviors such as **violent flailing or thrashing of arms and legs** (especially when movements are asynchronous or arrhythmic), **pelvic thrusting, head turning from side to side, bizarre vocalizations, weeping / whining** (highly specific for NES), **opisthotonus** (90% specific for NES), **trembling, eye fluttering, bilateral motor activity with preserved consciousness** are not seen in epileptic seizures (exception - complex partial frontal lobe seizures).

   *shaking with movements away from midline is unusual in true seizures.

   **exception: supplementary motor area seizures (mesial frontal area) but these seizures are usually tonic (not clonic)

• lateral tongue laceration is very specific for true seizures.
If any two of following are demonstrated, 96% of time this will be NES:

1. Out-of-phase clonic arm movement
2. Out-of-phase clonic leg movement
3. No vocalization or vocalization at start of event

Definitive diagnosis - inpatient simultaneous video-EEG recording (normal ictal EEG + excess of muscle artifact on normal background)

N.B. 30% complex partial seizures and 70% simple partial seizures are not accompanied by EEG changes! There are unusual seizures that may fool experts!

- **HISTORY** alone is usually not sufficient for definitive diagnosis; even experienced observers cannot distinguish epileptic from psychogenic seizures in > 50-80% cases!
  
  N.B. **10-75% patients also have true epilepsy**! - recording nonepileptic attacks in patient with uncontrolled seizures does not, by itself, prove that all patient's seizures are psychogenic.
  
  Verify with patient and family that recorded events are typical of habitual and disabling seizures experienced at home!

- serum [prolactin]↑ - following 15% simple seizures, 45-60% complex partial seizures, and 80-90% TCSs; serum is obtained within 10-30 minutes* of event and compared to interictal baseline level (drawn on different day at same time).
  
  — [prolactin]↑ is caused by widespread high frequency mesial temporal lobe discharges; [prolactin] stays normal in seizures not involving these limbic structures
  
  — NES may cause elevated cortisol levels but normal [prolactin] levels!
  
  — normal [prolactin] does not exclude epilepsy and is frequently seen with frontal lobe seizures!

  *i.e. peak levels are reached in 15-20 minutes, and gradually return to baseline over subsequent hour

- **psychological testing** may help: differences occur in ES and NES on Minnesota Multiphasic Personality Inventory (MMPI) scales in hypochondriasis, depression hysteria, and schizophrenia.
### Treatment

- Psychotherapy & pharmacological treatment of psychiatric disease.
  - Patient should be informed of diagnosis.
  - AEDs may worsen some pseudoseizures.

### Bibliography

For ch. “Epilepsy and Seizures” → follow this [Link](#)