EEG patterns in status epilepticus and coma

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Talk overview

- Anatomic localization and EEG pattern
- EEG patterns of acute encephalopathy
- EEG patterns in post cardiac arrest
- Ictal-interictal continuum EEG patterns
  - Which patterns warrant treatment?
- Ictal EEG patterns and criteria for nonconvulsive status epilepticus in comatose patients
Introduction

• The EEG has been available but often neglected as a quick, noninvasive, inexpensive, first test for evidence of organic confusion in favor of its use more specifically for seizures and epilepsy

  Kaplan PW and Sutter R; J Clin Neurophysiol 2013

• EEG enables rapid bedside electrophysiological monitoring providing dynamic real-time information on neocortical brain activity and dysfunction

  Sutter R et al; J Clin Neurophysiol 2015
Usefulness of EEG in critically ill patients

- Identifying epileptic states or interictal patterns
- Identifying whether altered mental status is because of
  - lateralized focal dysfunction
  - cortical or subcortical dysfunction
  - excessive sleepiness
  - problem of arousal
  - possible medication intoxication

** EEG may at times reveal the preponderant cause of encephalopathy e.g. TWs suggest that hepatic failure dominate the clinical picture**
Anatomic localization and EEG pattern
Investigations with clinical-EEG-imaging correlations should expedite appropriate triage and management of patients in the ICU, ER, and general ward.

Kaplan PW and Rossetti AO et al; J Clin Neurophysiol 2011
# TABLE 3. Anatomic Localization and EEG Pattern

<table>
<thead>
<tr>
<th>Anatomic Localization</th>
<th>EEG Frequency/Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>Decreased α amplitude</td>
</tr>
<tr>
<td></td>
<td>Slowing of posterior α background frequency</td>
</tr>
<tr>
<td>Subcortical/white matter</td>
<td>Increased polymorphic or arrhythmic δ-activity</td>
</tr>
<tr>
<td></td>
<td>TWs</td>
</tr>
<tr>
<td>Cortical and subcortical</td>
<td>Frontal intermittent δ-activity</td>
</tr>
<tr>
<td></td>
<td>Slow posterior basic rhythm (background activity) <em>with</em> slow-wave intrusion</td>
</tr>
<tr>
<td></td>
<td>(arrhythmic δ-activity)</td>
</tr>
<tr>
<td>Brain stem</td>
<td>Arrhythmic δ-activity, rhythmic δ-activity</td>
</tr>
<tr>
<td></td>
<td>Impaired arousal patterns</td>
</tr>
<tr>
<td></td>
<td>Spindle activity</td>
</tr>
</tbody>
</table>
Anatomic localization

- Slowing of EEG background activity without slow-wave activity in the delta range has been linked to **cortical impairments** that spare subcortical structures.
- **Subcortical/white matter abnormalities or hydrocephalus** can lead to projected slow-wave activity or to TWs.
- Clinical entities involving **both cortical and subcortical regions** (diffuse cerebral abnormalities) engender both background slowing and slow-wave activity.

*Kaplan PW and Rossetti AO et al; J Clin Neurophysiol 2011*
<table>
<thead>
<tr>
<th>Locations of the lesions</th>
<th>EEG findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse cortical and subcortical gray matter disease, whether or not this pathology was associated with lesions in the white matter</td>
<td>Generalized bilaterally synchronous paroxysmal discharges</td>
</tr>
<tr>
<td></td>
<td><em>(abnormal interactions between cortical and subcortical neuronal systems)</em></td>
</tr>
<tr>
<td>White matter diseases</td>
<td>Continuous non-paroxysmal polymorphic delta activity</td>
</tr>
<tr>
<td></td>
<td>Absence of paroxysmal discharges</td>
</tr>
<tr>
<td>Diffuse encephalopathies involving gray and white matters</td>
<td>Generalized bilaterally synchronous paroxysmal discharges</td>
</tr>
<tr>
<td></td>
<td>+ Continuous non-paroxysmal polymorphic delta activity</td>
</tr>
</tbody>
</table>

Gloor P et al; Electroenceph Clin Neurophysiol 1955
EEG patterns of acute encephalopathy
• Encephalopathy is a term often used by electroencephalographer, referred to as delirium in psychiatry and as altered mental status or acute confusional states in neurology.
Multiple symptoms of encephalopathy

Kaplan PW and Sutter R; J Clin Neurophysiol 2013
EEG patterns in acute encephalopathy

- FIRDA
- TWs
- Theta pattern
- Theta/delta pattern
- Polymorphic high-voltage delta pattern
FIRDA

- a repetitive appearance of up to 2 seconds of frontal rhythmic slow (delta) waves activity at < 4 Hz, usually is reactive to external noxious stimulation
- Generally reflects an old fixed structural problem (e.g., stroke)
FIRDA

• Transient intermittent rhythmic slow waves, 1.5-4 Hz, localized mainly over frontopolar regions
• Occurs in adults, in contrast with OIRDA
• Associated with mild to moderate diffuse encephalopathy particularly from renal failure and hyperglycemia
• Pathological hyperactivity occurring in diffuse gray matter disease, in both cortical and subcortical gray locations
• Old ischemic structural brain lesions may predispose some patients to develop FIRDA during acute metabolic derangement
• Deep midline lesions were present only in a minority of the patients
  Cobb’s (1945) lesions in the epithalamus produced “rhythmic delta activity”
The main deflection is downward, indicating a surface positive change. The main deflection is usually preceded and followed by low-amplitude negative deflections giving the whole complex a triphasic contour.
Clinical correlates

- TWs have been described in a large number of medical conditions including:
  - Metabolic encephalopathies
  - Dementia
  - Drugs (cephalosporin, lithium, levodopa, baclofen, valproic acid)
  - Paramedian thalamic infarction
  - Sepsis-associated encephalopathy
  - Hashimoto’s encephalopathy
- TWs are believed to reflect abnormal activity within thalamo-cortical circuits
• TWs are likely to be a marker of a single variable, but rather a result of a complex interplay of metabolic, toxic, infectious, and structural cerebral abnormalities that affect thalamo-cortical circuits.

Predominant brain abnormalities: white matter change (60%) and/or brain atrophy (55%)
Theta pattern

- Generalized slow background activity with a frequency of 4-7 Hz and amplitude of > 40 µV without intrusion of delta (<4 Hz) or alpha activity (8-13 Hz) for > 20% of the recording during wakefulness.
- Benign theta-dominant patterns with preserved background reactivity in patients with cortical dysfunction (dementia and mild-to-moderate encephalopathy), it can be seen without background reactivity to external stimulation in coma from hypoxic-ischemic brain injury and carries a poor prognosis.
Theta/delta pattern

• Generalized slow background activity of 4-7 Hz and amplitude of > 80 µV with intrusion of alpha activity for < 20% of the recording during wakefulness and intermixed with delta activity in 20-50% during drowsiness or arousal
Polymorphic high-voltage delta pattern

- Generalized slow background activity of <4 Hz and amplitude of > 80 µV with intrusion of theta or alpha activity for <20% of the recording during drowsiness or arousal
- Usually arises in more advanced states of encephalopathy as well as in coma and is predominantly reflected over the anterior regions but then tends to appear more diffusely as coma deepens
- Predominant structural abnormalities involve large areas of the subcortical white matter; however, severe metabolic derangements may also produce similar patterns and focal or unilateral delta activity usually associated with focal subcortical brain lesions
Progressive EEG changes

- Dosynchronization or fast activity
- Increase in voltage and rhythmicity, particularly delta-activity
- Mixtures of slower and faster frequencies and increased delta-activity with deeper levels
- Burst-suppression, with extension of the suppression phases with deeper sedation
- Suppression followed by isoelectric EEG

Level of sedation

min.  max.
Etiologies of specific EEG patterns in encephalopathy. Intracerebral hemorrhage (ICH) and increased intracranial pressure (ICP)

Kaplan PW and Sutter R; J Clin Neurophysiol 2013
Sutter R and Kaplan PW; J Clin Neurophysiol 2013
Clinical and imaging correlates of EEG patterns in encephalopathic patients (154 hospitalized patients)

<table>
<thead>
<tr>
<th>Imaging correlates</th>
<th>OR</th>
<th>Multivariate analysis p-value</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theta</td>
<td>2.6</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Brain atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theta/delta</td>
<td>6.8</td>
<td>0.005</td>
<td>Unfavorable (OR 2.5, p =0.033)</td>
</tr>
<tr>
<td>Intracerebral hemorrhages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRDA</td>
<td>2.7</td>
<td>0.004</td>
<td>Favorable (OR 4.8, p = 0.004)</td>
</tr>
<tr>
<td>Past CVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWs</td>
<td>6</td>
<td>0.004</td>
<td>Death (OR 4.5. p = 0.005)</td>
</tr>
<tr>
<td>Liver failure multi-organ failure</td>
<td>4</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>Alcohol/drug abuse with or without intoxication HIV infection</td>
<td>3.8</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

At discharge: GCS 1-3: unfavorable; GCS >3 : favorable outcome

Sutter R et al; J Neurol 2013
Proposed diagram for prognostication of outcome in encephalopathy

Kaplan PW and Sutter R; J Clin Neurophysiol 2013
Mean urea on day of EEG

OR for the presence of triphasic waves per unit: OR 1.26, 95%CI 1.01-1.04, p=0.004

Mean NH₃ on day of EEG

OR for the presence of triphasic waves per unit: OR 1.04, 95%CI 1.01-1.07, p=0.011

Sutter R et al; J Neurol 2013
Reactivity of the background activity

- A variety of forms of reactivity
  - an increase or decrease in amplitude
  - an increase or decrease in frequency
- EEG responsiveness (EEG change after sensory stimulation) is associated with greater chance of recovery than lack of reactivity
- Reactivity should be tested in all comatose patients, unless contraindicated because of concerns regarding raised intracranial pressure

Young GB et al; J Clin Neurophysiol 1999
Bedside testing for EEG reactivity

- **Auditory reactivity**: clapping or shouting in the patient’s ears
- **Somatosensory stimulation**: applying pressure to the nail bed of each hand and to the supraorbital nerve above the medial third of the eyebrow
- **Passive eye opening**: is recommended in suspected alpha coma

Young GB et al; J Clin Neurophysiol 2000
The most valid and reliable data on the predictive value of EEG background reactivity in coma comes from patients with hypoxic-ischemic brain injury after cardiac arrest, where the absence of EEG reactivity is highly predictive of poor outcome and death.

No reactivity EEG:
Sensitivity of 90% (95% CI 0.57-1) for not regaining awareness
Specificity of 94% (95% CI 0.7-1)

The lack of reactivity implies widespread damage to the ARAS

Table 3: EEG Reactivity and Outcome of Patients

<table>
<thead>
<tr>
<th>No. of patients with reactivity</th>
<th>No. of patients with no awareness</th>
<th>No. of patients with awareness</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Thenayan et al; J Crit Care 2010
• There is weak evidence for the predictive value of unreactive EEG in patients with nonhypoxic encephalopathy

Sutter R and Kaplan PW; Clin EEG and Neurosci 2015
Rossetti AO et al; Ann Neurol 2010
In acute nonhypoxic encephalopathy

Univariate analysis: older age, intracranial hemorrhage, coma (GCS ≤ 8), and nonreactive EEG background activity were independently associated with death

Multivariate analysis: only nonreactive EEG background activity was associated with death
Whilst EEG sleep elements were detected more frequently in patients favorable outcome, only K-complexes were significantly and independently associated with good outcome in ICU patients with acute encephalopathy.

Each sleep element comes from a different cerebral source and may carry some distinct prognostic value.

K-complexes: correspond to signal in primary sensory cortex.
EEG patterns in post cardiac arrest
10 yo girl with coma after cardiac arrest

The day of cardiac arrest

The day after

The temporal dynamic changes of EEG pattern over time in patients with post cardiac arrest

5 days after

Bauer G et al; J Clin Neurophysiol 2013
Malignant EEG patterns in post cardiac arrest

- Generalized low voltage EEG
- Burst suppression
- Alpha and theta coma
- Generalized periodic discharges

Thenayan et al; J Crit Care 2010
Fugate JE et al; Ann Neurol 2010
EEG within 24 hours is a robust contributor to prediction of poor or good outcome of comatose patients after cardiac arrest, despite the use of mild therapeutic hypothermia and sedative medication.

Rapid recovery toward continuous patterns within 12 h is strongly associated with a good neurological outcome.

Hofmeijer J et al; Neurology 2015
Thenayan et al; J Crit Care 2010

Generalized suppression (< 10 uV) or burst suppression with epileptiform activity are indicators of failure to gain awareness after cardiac arrest.

Table 1
Malignant EEG patterns are II to V

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>I. Delta/theta &gt;50% of recording (not theta coma)</td>
</tr>
<tr>
<td></td>
<td>A. With reactivity</td>
</tr>
<tr>
<td></td>
<td>B. Without reactivity</td>
</tr>
<tr>
<td>Malignant</td>
<td>II. Triphasic waves</td>
</tr>
<tr>
<td></td>
<td>III. Burst-suppression pattern</td>
</tr>
<tr>
<td></td>
<td>A. With epileptiform activity</td>
</tr>
<tr>
<td></td>
<td>B. Without epileptiform activity</td>
</tr>
<tr>
<td></td>
<td>IV. Alpha/theta/spindle pattern coma (no reactivity)</td>
</tr>
<tr>
<td></td>
<td>A. &lt;20 but &gt;10 μV</td>
</tr>
<tr>
<td></td>
<td>B. &lt;10 μV</td>
</tr>
<tr>
<td></td>
<td>V. Suppression (generalized)</td>
</tr>
</tbody>
</table>

Table 2
EEG Patterns and Patient Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. of patients with no awareness</th>
<th>No. of patients with awareness</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with malignant EEG pattern</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>No. of patients with benign EEG pattern</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>EEG Feature</th>
<th>Prognosis Significance</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous background</td>
<td>Regaining consciousness</td>
<td>100% specificity in NT (Rundgren et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>Good outcome (CPC 1–2)</td>
<td>0.91 PPV in TH (Rundgren et al., 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% specificity (Cloostermans et al., 2012)</td>
</tr>
<tr>
<td>Burst-suppression</td>
<td>Mortality</td>
<td>100% specificity in TH (Rundgren et al., 2010; Sadaka et al., 2014)</td>
</tr>
<tr>
<td>Burst-suppression with identical bursts</td>
<td>Poor outcome (GOS 1–3)</td>
<td>100% specificity at any time (Sivaraju et al., In press)</td>
</tr>
<tr>
<td>Isoelectric or low voltage</td>
<td>Poor outcome (CPC 3–5)</td>
<td>100% specificity (Cloostermans et al., 2012)</td>
</tr>
<tr>
<td>No reactivity</td>
<td>Death</td>
<td>100% specificity (Hofmeijer et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>No awareness recovery</td>
<td>94% specificity (Thenayan et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>93% specificity in NT (Rossetti et al., 2010a)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Poor outcome (CPC 3–5)</td>
<td>100% specificity in NT (Tsetsou et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>94% specificity (Legriel et al., 2013)</td>
</tr>
<tr>
<td>Epileptiform transients</td>
<td>Poor outcome (CPC 3–5)</td>
<td>100% specificity (Rittenberger et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>92% specificity (Rossetti et al., 2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% specificity (Rossetti et al., 2012)</td>
</tr>
</tbody>
</table>

CPC, cerebral performance category; GOS, Glasgow Outcome Score; NT, normothermia; PPV, positive predictive value; TH, therapeutic hypothermia.
BS without identical bursts

BS with identical bursts

Hofmeijer J et al; Clin Neurophysiol 2014
Ictal-interictal continuum (IIC) EEG patterns
IIC EEG patterns

- **Rhythmic delta activity (RDA):** LRDA, GRDA
- **Periodic discharges (PDs):** LPD, GPD, BiPD, MfPD
- **Spike or sharp wave discharges (SW):**
Periodic lateralized epileptiform discharges (PLEDs)

- PLEDs are highly associated with seizures
- Incidence of seizures in the acute setting of PLEDs to be 58-100%
- PLEDs were associated with an **acute process** and occurred early during the course of illness
- PLEDs have been associated with focal destructive lesions
  - Acute infarction (most common)
  - Infections
  - Hematomas
  - Tumors

Combined pre-existing structural lesion with a metabolic disturbance

PLEDs can be also seen after status epilepticus in patients with chronic epilepsy

PLEDs

- **Associated clinical seizures**: repetitive focal motor seizures or *epilepsia partialis continua*
- Repetitive confusional states due to complex partial status epilepticus were also in some patients with PLEDs
- The prognosis of patients with PLEDs is largely determined by the underlying disease process. Acute stroke appears to be associated with the worst prognosis, with mortality rates ranging from 28.8% to 53%
PLEDs-proper versus PLEDs-plus

- **PLEDs-plus**: required an accompanying low amplitude rhythmic discharge
- **Higher rate of seizure in PLEDs-plus**
  - 74% of the 50 patients with PLEDs-plus
  - 6% of the 34 patients with solely PLEDs-proper

Reiher J et al; Electroencephalogr Clin Neurophysiol 1991
Bilateral independent PLEDs (BIPLEDs)

- Bilateral asynchronous PLEDs
- Highly associated with seizures (78%) (18 patients)
- BIPLEDs were typically related to acute structural lesions with or without metabolic disturbance

De la Paz and Brenner; Arch Neurol 1981
Etiology

- Anoxic encephalopathy
- CNS infection
- Chronic epilepsy

De la Paz and Brenner; Arch Neurol 1981

The clinical state and prognosis with BIPLEDs may be worse than with PLEDs; however, it should be kept in mind that this conclusion is based on small numbers of reported cases.
Generalized periodic epileptiform discharges (GPEDs)

- Generalized, synchronous, periodic or near periodic complexes that occupied at least 50% of a standard 20 minute EEG
- Periodic sharp, slow, and triphasic-like waves, and combinations thereof
- Excluded suppression-burst complexes, triphasic waves, FIRDA

Husain AM et al; J Clin Neurophysiol 1999
Etiologies

- Anoxia and toxic-metabolic encephalopathy (40%)
- Primary neurologic process (32%)
- Toxic-metabolic encephalopathy (28%)

Husain AM et al; J Clin Neurophysiol 1999
GPEDs

• Relationship to status epilepticus:
  8 (32%) out of 25 patients met criteria for SE

• Prognosis:
  Nine patients (36%) were alive at the time of discharge, whereas 16 of 25 (64%) had died

Husain AM et al; J Clin Neurophysiol 1999
The ictal significance of GPEDs post cardiac arrest is under debate:
- whether this EEG pattern represents irreversible hypoxic brain damage (thereby futile to treat)
- or
- potentially nonconvulsive status epilepticus (thereby potentially treatable)
Prognostic significance of GPEDs

36 postcardiac patients with hypoxic encephalopathy; 24 with GPEDs, 12 with BIPLEDs; 10/36 pts survived

- GPEDs carry a grave clinical prognosis following cardiac arrest

Robeiro A et al; Epilepsy & Behav 2015
52 patients with hypoxic encephalopathy: 14 patients had either GPEDES (6 pts) or BiPLEDs (8 pts); All 14 pts were comatose and died

Aggressive treatment of patients may not be warranted when these EEG patterns are seen after anoxic brain injury

Table 1
Clinical findings, neuroimaging studies and outcome of the 14 patients with BiPLEDs and GPEDES and HE.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Type of PED</th>
<th>Diagnosis</th>
<th>MR/CT (abnormal)</th>
<th>Localization: Cortical</th>
<th>Mental status: Coma</th>
<th>Clinical seizures at onset</th>
<th>SE</th>
<th>AED therapy</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>M</td>
<td>BiPLED</td>
<td>Laceration myocardal</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>PRO, PHT</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>F</td>
<td>BiPLED</td>
<td>Heroin overdose</td>
<td>+</td>
<td></td>
<td>Focal</td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>BiPLED</td>
<td>Myocardial infarction</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO, PHT</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>F</td>
<td>BiPLED</td>
<td>Myocardial infarction</td>
<td>+</td>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td>PRO, PHT, DZP</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>F</td>
<td>BiPLED</td>
<td>Cardiogenic shock</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO, CNZ, FHT, LEV, VPA</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>M</td>
<td>BiPLED</td>
<td>Ventricular tachycardia</td>
<td>NTP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO, PHT, VPA, CNZ</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>M</td>
<td>BiPLED</td>
<td>Myocardial infarction</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO, GBP</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>F</td>
<td>BiPLED</td>
<td>Laceration myocardal</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PB, PHT</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>M</td>
<td>GPEDE</td>
<td>Carbon monoxide poisoning</td>
<td>+</td>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td>PRO, CNZ</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>M</td>
<td>GPEDE</td>
<td>Myocardial infarction</td>
<td>+</td>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>F</td>
<td>GPEDE</td>
<td>Bithalamic stroke</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>M</td>
<td>GPEDE</td>
<td>Respiratory failure</td>
<td>+</td>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>37</td>
<td>M</td>
<td>GPEDE</td>
<td>Ventricular tachycardia</td>
<td>NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>F</td>
<td>GPEDE</td>
<td>Ventricular tachycardia</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRO</td>
<td>+</td>
</tr>
</tbody>
</table>

(?) Not performed; SE, status epilepticus; PRO, propofol; PHT, phenytoin; DZP, diazepam; CNZ, clonazepam; LEV, levetiracetam; VPA, valproate; FB, phenobarbital; GBP, gabapentine.

CT head normal.
Prognostic significance of GPEDs

- GPDs on a suppressed background pattern are strongly associated with a poor outcome, whereas patients with GPDs on a continuous, normal amplitude background may occur.

Bauer G et al; J Clin Neurophysiol 2013
Pathophysiology of GPDs

- The glutamatergic synapse of excitatory pyramidal cells to inhibitory interneurons is relatively sensitive to hypoxia.
- Selective synaptic failure or neuronal damage of inhibitory interneuron, leading to disinhibition of excitatory pyramidal cells, presumably plays a critical role.

Van Putten and Hofmeijer J et al; Epilepsy & Behav 2015
Fig. 2. (Left) Meanfield model used to simulate generalized periodic discharges (GPDs). Pyramidal cells receive both excitatory afferent input and, with a brief delay, inhibitory input from the same presynaptic source (feed-forward inhibition). (Right) Top panel: EEG recording from a patient after cardiac arrest showing GPDs. Bottom panel: simulated EEG showing GPDs. In this simulation, the number of synapses from pyramidal cells to interneurons was selectively reduced to 90%, while the number of other synapses was unchanged. The dominant frequency is similar (~2.5 Hz).

Illustration slightly modified from [32].
SIRPIIDs (Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges)

• SIRPIIDs are commonly elicited by stimulation in critically ill (stuporous or comatose), encephalopathic patients
• Pathophysiology of SIRPIIDs is unknown
• The relationship between clinical seizures and SIRPIIDs is unclear, although some association is found between SIRPIIDs and clinical status epilepticus
• Whether these discharges contribute to neuronal injury or altered mental status is uncertain
SPECT–Negative SIRPIDs Argues Against Treatment as Seizures

Steven R. Zeiler,* Lisa C. Turtzo,† and Peter W. Kaplan‡

Zieler SR et.al; J Clin Neurophysiol 2011

SPECT-Negative SIRPIDs: Less Aggressive Neurointensive Care?

Christina C. Smith,* William O. Tatum,† Vivek Gupta,‡ Robert A. Pooley,§ and William D. Freeman*†

Smith CC et.al; J Clin Neurophysiol 2014
However, the pace of technological advances that now allows long-term recording of video-EEG has not been matched by that of increased understanding of the pathophysiology that creates the myriad of ambiguous but potentially ictal patterns, their clinical implications, or how aggressively to treat them.

Chong DJ and Hirsch LJ et al; J Clin Neurophysiol 2005
### EEG patterns and their correlation with NCS/NCSE

<table>
<thead>
<tr>
<th>EEG patterns</th>
<th>Do NOT reflect NCSE (NOT TREATED)</th>
<th>Reflect NCSE (Should be TREATED)</th>
<th>BORDERLINE Of NCSE in coma One additional criteria is needed to diagnose NCSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical coma pattern</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diffuse polymorphic delta activity</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spindle coma</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alpha/theta coma</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Low voltage</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Burst suppression</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ictal patterns with typical spatiotemporal evolution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epileptiform discharges &gt; 2.5 Hz in comatose patients</strong></td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td><strong>GPDs or LPDs &lt; 2.5 Hz</strong></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td><strong>Rhythmic discharges (RDs) &gt; 0.5 Hz</strong></td>
<td></td>
<td></td>
<td>×</td>
</tr>
</tbody>
</table>
Fig. 2. The relationship of the depth of coma and the contribution of the epileptic activity during nonconvulsive status epilepticus (modified from 14, Fig. 11). Abbreviations: AS: absence status epilepticus, EPC: epilepsy partialis continua, GPDs: generalized periodic discharges, IGE: idiopathic generalized epilepsy, LPDs: lateralized periodic discharges, NCSE: nonconvulsive status epilepticus.
Coma with epileptiform discharges (Coma-EDs)

- Prior deciding treat or not treat the observed EEG patterns, clinician has to answer the following questions

1) Is the coma caused by SE or by the underlying brain condition itself?
2) To what degree does the epileptic activity contribute to the depth of coma?
3) Does the ongoing epileptic activity worsen the prognosis?
<table>
<thead>
<tr>
<th></th>
<th>PLEDs</th>
<th>BI-PLEDs</th>
<th>GPEDs</th>
<th>PSIDDS</th>
<th>PLIDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-discharge interval</td>
<td>Typical: 0.5 to 4 s, up to 8 s</td>
<td>Typical: 0.5 to 4 s, up to 8 s</td>
<td>0.5–4 s</td>
<td>4–30 s</td>
<td></td>
</tr>
<tr>
<td>Topography</td>
<td>Lateraled (contralateral spread common)</td>
<td>Independently lateraled</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td>Rate of focal or tonic-clonic seizures</td>
<td>High, approximately 80%</td>
<td>Typically lower than in PLEDs but still high</td>
<td>Variable/unclear but not rare</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Associated myoclonus</td>
<td>Rare</td>
<td>Rare</td>
<td>Common with CJD but often not time-locked</td>
<td>Common with SSPE, time-locked</td>
<td></td>
</tr>
<tr>
<td>Mental status</td>
<td>Altered</td>
<td>Altered</td>
<td>Altered</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Outcome*</td>
<td>Variable*</td>
<td>Variable*</td>
<td>Variable*</td>
<td>Variable*</td>
<td></td>
</tr>
<tr>
<td>Morphology/other characteristics</td>
<td>Morphology variable. Associated with EPC</td>
<td>Morphology variable</td>
<td>Sharp waves, spikes, polyspikes, or sharply-contoured delta waves</td>
<td>Variable; often complex, stereotyped, polyphasic bursts, lasting 0.5–3 s</td>
<td></td>
</tr>
</tbody>
</table>
| Etiology               | Acute structural lesion: Infarct, ICH, tumor, infection; occasionally no lesion. After SE. Increased risk with metabolic disturbance. HSE | Anoxia, bilateral acute lesions. Occasionally unilateral or no lesion apparent. HSE | Metabolic encephalopathy, anoxia. NCSE. After SE. Lithium, baclofen, CJD | Toxins (PCP, ketamine barbiturates, anesthetics), anoxia SSPE
The Ictal-Interictal-Injury Continuum

Potential for 2° Neuronal Injury

High

Interictal

Ictal

S-B

TW

GPEDs

PLEDs proper

SIRPIDs

PLEDs-Plus

EPC

NCS

NCSE

GCSE
• Periodicity was thought to have been caused by disconnection of the cortex from subcortical structures, usually secondary to a large white matter lesion

Cobb W and Hill D; Brain 1950

• The majority of the patients (64.7%) had lesions of cortical gray and subcortical white matters

Gurer G et al; Clin EEG Neurosci 2004
American Clinical Neurophysiology Society’s Standardized Critical Care EEG Terminology: 2012 Version

- No uniformly accepted nomenclature for EEG patterns frequently encountered in critically ill patients
- No consensus on which patterns are associated with ongoing neuronal injury, which patterns need to be treated, or how aggressively to treat them

Hirsch LJ et al; J Clin Neurophysiol 2013
Proposed nomenclature

A. Rhythmic or periodic patterns
B. Minimal time epochs to be reported. Documented separately
   - First 30 minutes
   - Each 24 hour period
C. Quantification and categorization of sporadic (non-rhythmic and non-periodic) epileptiform discharges (includes sharp waves and spikes)
D. Background EEG

Hirsch LJ et al; J Clin Neurophysiol 2013
Rhythmic or periodic patterns

- Main term 1
  - Generalized (G)
  - Lateralized (L) (further specify whether unilateral or bilateral asymmetric)
  - Bilateral independent (BI)
  - Multifocal (Mf)
• Main term 2
  ➢ Periodic discharges (PDs): presence of inter-discharge interval
  ➢ Rhythmic delta activity (RDA)
  ➢ Spike-and-wave or sharp-and-wave (SW)

No interval between consecutive waveforms
<table>
<thead>
<tr>
<th>OLD Term</th>
<th>NEW Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphasic waves, most of record</td>
<td>continuous 2/s GPDs (with triphasic morphology)</td>
</tr>
<tr>
<td>PLEDs</td>
<td>LPDs</td>
</tr>
<tr>
<td>BIPLEDs</td>
<td>BIPDs</td>
</tr>
<tr>
<td>GPEDs/PEDs</td>
<td>GPDs</td>
</tr>
<tr>
<td>FIRDA</td>
<td>Occasional frontally predominant brief 2/s GRDA (if 1-10% of record)</td>
</tr>
<tr>
<td>PLEDS+</td>
<td>LPDs+</td>
</tr>
<tr>
<td>SIRPIDs* w/ focal evolving RDA</td>
<td>SI-Evolving LRDA</td>
</tr>
<tr>
<td>Lateralized seizure, delta frequency</td>
<td>Evolving LRDA</td>
</tr>
<tr>
<td>Semirhythmic delta</td>
<td>Quasi-RDA</td>
</tr>
</tbody>
</table>

*SIRPIDs = stimulus-induced rhythmic, periodic or ictal discharges.
Ictal EEG patterns and criteria for nonconvulsive status epilepticus in comatose patients
Table 1: Criteria for seizure

**Guideline:** To qualify at least one of primary criteria 1–3 and one or more of secondary criteria, with discharges >10 seconds

**Primary criteria**

1. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at >3/second.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/second and secondary criterion #4.
3. Sequential rhythmic waves and secondary criteria 1, 2 and 3 with or without 4.

**Secondary criteria**

1. Incrementing onset: increase in voltage and/or increase or slowing of frequency.
2. Decrementing offset: decrease in voltage or frequency.
3. Post-discharge slowing or voltage attenuation.
4. Significant improvement in clinical state or baseline EEG after anti-epileptic drug.

Young GB et al; Neurology 1996
### TABLE 2. Criteria for Non-Convulsive Seizure

Any pattern lasting at least 10 seconds satisfying any one of the following 3 primary criteria:

**Primary Criteria:**

1. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at \( \geq 3/\text{sec} \).
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at \( <3/\text{sec} \) and the secondary criterion.
3. Sequential rhythmic, periodic, or quasi-periodic waves at \( \geq 1/\text{sec} \) and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/sec, e.g. from 2 to 3/sec), morphology, or location (gradual spread into or out of a region involving at least 2 electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not adequate to satisfy evolution in morphology.

**Secondary criterion:**

Significant improvement in clinical state or appearance of previously-absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled to acute administration of a rapidly-acting AED. Resolution of the “epileptiform” discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns would not satisfy the secondary criterion.

AED = antiepileptic drug; Modified from (Young et al. 1996).

*Chong DJ and Hirsch LJ et al; J Clin Neurophysiol 2005*
<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Salzburg Consensus Criteria for nonconvulsive status epilepticus (SCNC) [1].</td>
</tr>
</tbody>
</table>

Patients without known epileptic encephalopathy
- EDs > 2.5 Hz, or
- EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) AND one of the following:
  ○ EEG and clinical improvement after IV AEDs*, or
  ○ Subtle clinical ictal phenomena, or
  ○ Typical spatiotemporal evolution**

Patients with known epileptic encephalopathy
- Increase in prominence or frequency when compared with baseline with observable change in clinical state
- Improvement of clinical and EEG features with IV AEDs*

*If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE
**Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency)

EDs: epileptiform discharges (spikes, polyspikes, sharp waves, and sharp-and-slow-wave complexes)
IV AEDs: intravenous antiepileptic drugs

Trinka U and Leitinger M; Epilepsy & Behav 2015
clinical suspicion of NCSE (without preexisting epileptic encephalopathy)

**EEG data**

- frequency of epileptiform discharges >2.5 Hz
- typical ictal spatio-temporal evolution
- subtle ictal clinical phenomena
  - 4a) EDs <2.5Hz with fluctuation, or
  - 4b) RA >0.5 Hz with fluctuation, or
  - 4c) RA >0.5 Hz without fluctuation

**clinical data**

- transition from premorbid to current ill state within minutes to hours
- patient did not improve significantly in last minutes to hours, apart from waxing and waning
- no information from brain imaging sufficiently explaining EEG-pattern (e.g. brain stem haemorrhage)
- no metabolic/toxicologic derangement sufficiently explaining EEG-pattern (e.g. acute renal or liver failure)

---

ED...epileptiform discharge
RA...rhythmic activity
dclin...clinical
IV AED...intravenous antiepileptic drug
NCSE...non-convulsive status epilepticus

---

important note regarding improvement to IV AED:
- for clinical practice: all four constellations qualify for NCSE.
- for research projects: patient qualifies for NCSE if EEG and/or clinical improvement

---

EEG data AND clinical data appropriate

---

“NCSE”

---

Fig. 12. Algorithm for diagnosis of nonconvulsive status epilepticus with the modified Salzburg Consensus Criteria for NCSE (mSCNC) (see text for further details) [152].

Trinka U and Leitinger M; Epilepsy & Behav 2015
Thank you for your attention