Summary

Electroencephalography (EEG) has long been used in evaluating comatose patients, and is being increasingly found to uncover patterns of prognostic significance, reveal subclinical seizure activity and provide data during treatment in which patients are paralyzed. Some EEG patterns reveal increasing degrees of cerebral compromise with progressive slowing of the background frequencies, while others can be explored for reactivity to external stimuli for prognostic purposes. With some etiologies, particular patterns carry grave import such as flat or highly suppressed patterns, or unreactive alpha, delta or burst-suppression patterns. Others including beta and triphasic patterns may herald a good prognosis, depending on cause. A working knowledge of these EEG patterns with their extenuating features can supplement the imaging and clinical examination information available to the treating physician.

Key words: Alpha coma, beta coma, theta coma, continuous high-voltage delta coma, spindle coma, burst-suppression, low-voltage, slow and nonreactive coma, electro-cerebral inactivity, periodic EEG coma patterns, electroencephalography, neurocritical care

Electroencephalographic Patterns in Coma: When Things Slow Down

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Les tracés EEG à l’état comateux : quand tout ralentit

L’électroencéphalographie (EEG) est utilisée depuis pas mal de temps pour évaluer les patients comateux. De plus en plus de tracés EEG importants pour le pronostic, révélateurs de crises épileptiques subcliniques et indicateurs de pistes thérapeutiques sont identifiés chez les patients paralysés. Certains tracés permettent de conclure à une complication cérébrale progressive d’raison d’un ralentissement progressif, tandis que d’autres tracés ont une valeur pronostique, en particulier à cause de la réactivité aux stimuli externes. Certaines modifications de l’EEG sont significatives en relation avec des étiologies déterminées, par exemple un aplatissement net de la courbe, une suppression marquée, un tracé alpha non réactionnel, un tracé delta ou de burst suppression. Selon la cause sous-tendante, d’autres modifications de l’EEG seront des indices pronostiques plutôt favorables, par exemple un tracé bêta ou l’apparition d’ondes triphasiques. Une connaissance approfondie de ces tracés EEG et de leurs caractéristiques supplémentaires peut apporter aux cliniciens un complément d’informations précieuses pour étayer les résultats d’un examen clinique ou d’imagerie.

Mots clés : Coma de niveau alpha, coma de niveau bêta, coma de niveau thêta, coma de niveau delta à haut vol-
Electroencephalographic Patterns in Coma...

Early insights

Early studies on stupor and coma [8] have correlated decreases in mental status and deepening levels of coma with particular EEG patterns and suppression of EEG reactivity. Initial case studies have reported EEG features associated with toxic, metabolic, ischemic, anoxic and endocrine disorders. Patterns recognized early on included predominant delta patterns, diffuse severe suppression, intermittent rhythmic delta activity, including frontal varieties (FIRDA) [9–14], triphasic waves [15–20], alpha frequency patterns in coma [21–33], and spindle-like sleep patterns in coma [33–41]. With worsening metabolic encephalopathies, EEG background amplitudes were seen to increase while dominant frequencies of background activity decreased. In the early 1960s, investigators noted the association between slowing of EEG activity and clinical evidence of cerebral cortical neuronal activity [42]. Comparable findings were noted by Stockard and Bickford, who found progressive EEG frequency slowing with progressive anesthesia [43] (Figure 1).

Clinical importance of EEG in comatose patients

Although EEG was increasingly looked at to provide objective evidence of brain dysfunction, it became evident that it provided little in the way of diagnostic specificity to an underlying cause. From another perspective, however, when used in specific etiologies of coma encountered in the intensive care unit, EEG has been progressively seen as providing a helpful tool in prognosis [44], revealing subclinical seizure activity, and tracking brain activity while patients are paralyzed [45–49]. To date, EEG is of greatest value in prognostication following closed traumatic brain injury [50] and cardio-respiratory arrest (CRA) with consequent hypoxic-ischemic encephalopathy [51, 52]. Recently, good outcome in comatose patients after CRA was shown to correlate well with EEG background variability and reactivity to stimulation during or after mild therapeutic hypothermia (MTH), or conversely herald poor outcome when evidence of reactivity to noxious stimuli was absent (Table 1). Advances in quantitative EEG during MTH after CRA recently identified subgroups of patients with distinct evolutions of qEEG “burst-suppression ratios” that were likely to have good neurofunctional recovery [53]. Several studies reported associations of a range of etiologies with particular EEG patterns in coma, providing some prognostic significance and guidance for prognosis that are presented below and summarized in Table 2.

Electroencephalographic frequency patterns in coma and their clinical context

Frequencies of background activity, such as alpha, theta, delta, or beta may predominate in different encephalopathies in coma, along with varying EEG background reactivity (changes in frequency, spatial distribution or amplitude) to external noxious stimuli. An excellent approach to EEG patterns and their associations with outcome in conjunction with background activity and reactivity in coma can be found in the work of Hussein [54], with a similar approach used here.

Beta coma

Generalized 12-16 Hz background activity is maximally seen over the frontal regions in patients with beta coma [55]. This activity can be intermixed with or without sleep spindle-like activity, alpha, or even delta activity (Figure 2A). Background reactivity to noxious stimulation can be preserved. However, there may be no EEG reactivity in deep coma [54, 56]. Beta coma can be seen in patients with intoxication

Introduction

Coma is an eyes-closed state of unresponsiveness with severely impaired arousal and cognition. It represents a failure of neurologic function resulting from damage of a critical number of brainstem and diencephalic pathways, which regulate the overall level of cortical function. Coma has been identified as a major predictor of death and poor neurofunctional outcomes in patients with a variety of critical illnesses, including ischemic strokes [1], intracerebral hemorrhage [2], traumatic brain injury [3, 4], hypoxic encephalopathy after cardiac arrest [1, 5, 6], and metabolic derangements or sepsis [1]. Besides ventilator dependency and infectious complications, coma is one of the major critical conditions leading to prolonged intensive care and increased mortality [7]. Cerebral electrographic patterns allow distinction of coma from normal sleep and other causes of confusion or unresponsiveness. Some EEG patterns reflect a deepening or lightening of mental status, though progression of coma through various EEG patterns is inconsistent. Several EEG patterns indicate the type of cerebral impairment, while others may suggest favorable or unfavorable prognoses.

This review presents different abnormalities of EEG patterns and background activity seen in coma, along with those that indicate deepening coma and have particular prognostic significance.
**Table 1: Predictive value of EEG background reactivity in comatose patients following cardiac arrest**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Time of examination</th>
<th>EEG background reactivity*</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossetti et al., 2010</td>
<td>Prospective study</td>
<td>34 patients</td>
<td>After CPR and during therapeutic hypothermia</td>
<td>Absent</td>
<td>False-positive rate 0% during hypothermia for poor outcome</td>
</tr>
<tr>
<td>Rossetti et al., 2010</td>
<td>Prospective study</td>
<td>111 patients</td>
<td>In the first 3 days after CPR and therapeutic hypothermia</td>
<td>Absent</td>
<td>False-positive rate 7% for poor outcome</td>
</tr>
<tr>
<td>Thenayan et al., 2010</td>
<td>Prospective study</td>
<td>29 patients</td>
<td>After CPR and with or without therapeutic hypothermia</td>
<td>Preserved</td>
<td>10/11 patients with reactivity regained awareness</td>
</tr>
<tr>
<td>Rossetti et al., 2012</td>
<td>Prospective study</td>
<td>61 patients</td>
<td>After CPR and during therapeutic hypothermia</td>
<td>Absent</td>
<td>False-positive rate 0% during and after hypothermia for poor outcome</td>
</tr>
<tr>
<td>Howard et al., 2012</td>
<td>Prospective study</td>
<td>39 patients</td>
<td>At a mean of 5 days after CPR</td>
<td>Absent or periodic generalized phenomenon</td>
<td>Significant association with poor outcome (False-positive rate not provided)</td>
</tr>
</tbody>
</table>

CPR = cardiopulmonary resuscitation; EEG = electroencephalography; cEEG = continuous electroencephalography
* to external noxious stimulation

**Figure 1: Progressive EEG changes with increasing level of sedation**
Table 2: Etiologies and prognosis of different electroencephalographic coma patterns

<table>
<thead>
<tr>
<th>Coma pattern</th>
<th>Etiologies</th>
<th>EEG background reactivity*</th>
<th>Most frequent outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta coma</strong></td>
<td>Intoxications or withdrawal (barbiturates or benzodiazepines), severe hyperthyroidism, Brainstem lesions</td>
<td>+ / -</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>Intermingled with delta activity</td>
<td>-</td>
<td>unfavorable</td>
</tr>
<tr>
<td><strong>Alpha coma</strong></td>
<td>Intoxication (barbiturates, benzodiazepines, anesthetic agents, meprobamate, imipramine) Brainstem lesions, locked-in syndrome</td>
<td>+ / -</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>More diffusely</td>
<td>+ / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td></td>
<td>Monomorphic posterior</td>
<td>+ / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td><strong>Theta coma</strong></td>
<td>Hypoxic-ischemic encephalopathy</td>
<td>(+) / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td><strong>High-voltage delta coma</strong></td>
<td>Metabolic encephalopathies, focal or unilateral white matter lesions</td>
<td>+</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>More diffusely</td>
<td>(+) / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td><strong>Spindle coma</strong></td>
<td>Traumatic brain injury, intracerebral hemorrhage, post-ictal states, intoxication</td>
<td>+</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>Theta and delta activity with paroxysmal bursts symmetric spindles</td>
<td>(+) / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td></td>
<td>Theta and delta activity with paroxysmal bursts of symmetric spindles</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Burst-suppression</strong></td>
<td>Intoxication (sedative drugs), anesthetic drug use, and hypothermia</td>
<td>+ / (-)</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>Theta and delta activity with intrusions of alpha and beta activity</td>
<td>(+) / - (controversial for outcome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theta and delta activity without intrusions of higher frequency activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low-voltage delta coma</strong></td>
<td>Traumatic brain injury, healthy individuals</td>
<td>+</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>Hypoxic-ischemic encephalopathy, severe traumatic brain injury</td>
<td>(+) / -</td>
<td>unfavorable</td>
</tr>
<tr>
<td><strong>Electro-cerebral inactivity</strong></td>
<td>Marked hypothermia, severe intoxications (nervous system depressant drugs)</td>
<td>-</td>
<td>favorable</td>
</tr>
<tr>
<td></td>
<td>Hypoxic-ischemic encephalopathy</td>
<td>-</td>
<td>unfavorable</td>
</tr>
</tbody>
</table>

* = preserved EEG background activity, - = no EEG background activity EEG = electroencephalography.
or withdrawal from sedating drugs, such as barbiturates or benzodiazepines [57, 58] but can also occasionally occur with brainstem lesions [59]. Following medication, beta coma is largely reversible and hence has a good prognosis if patients can be medically supported during the acute intoxication [56].

Alpha coma

Electroencephalographic patterns in unarousable patients that lie in the alpha frequency range (8-13 Hz) define alpha coma. Alpha activity is mostly seen over the frontal areas (Figure 2 B) [55]. However, the EEG alpha distribution and outcome depends largely on the etiology.

Reactive alpha patterns usually emerge after drug overdoses and lead to recovery in up to 90%. Alpha coma can also be seen in toxic encephalopathies [30, 57, 60, 61]. Intoxication is usually caused by barbiturates, benzodiazepines, anesthetic agents and anxiolytic agents [62]. EEG background reactivity is usually preserved and outcome tends to be good [61]. In contrast, posterior predominance is seen in comatose patients with brainstem lesions and varies often with external stimuli, but has a poor prognosis. Alpha frequency patterns appear more diffusely with hypoxic-ischemic encephalopathy after CRA and background reactivity to external stimuli is usually absent. Outcome is mostly poor with mortality exceeding 90% [31, 60, 61].

Theta coma

Theta coma refers to a diffuse background activity of 4-7 Hz in coma. This pattern may occur with or without intermixed alpha or delta activity (Figure 2 C) [31, 63].

Aside from “benign” theta dominant patterns in patients with cortical dysfunction, such as in dementia or mild to moderate encephalopathy [64], it can be seen in conjunction with hypoxic-ischemic brain injury and carries a poor prognosis [65]. Diffuse and unreactive theta activity appears most prominently over the anterior regions and usually carries a poor prognosis.

High-voltage delta coma

High-voltage delta activity in coma is defined as a background activity of 1-3 Hz with amplitudes that sometimes reach several 100 µV (Figure 2 D). Delta pattern coma may exhibit polymorphic shape or more rhythmic, blunted triphasic waves.

Although this pattern is usually seen in late stages of coma, reaction to noxious stimuli is mostly preserved. However, when coma further deepens, background reactivity to external stimuli decreases and becomes unreactive. These patterns usually arise with
more advanced states of encephalopathy as well as in coma, and are predominantly reflected over the anterior regions, but then tend to appear more diffusely as coma deepens. The predominant structural abnormalities involve large areas in the subcortical white matter; however, severe metabolic derangements may also produce similar patterns [54, 62, 66] and focal or unilateral delta activity usually is the expression of focal subcortical brain lesions. Overall, high-voltage delta activity is associated with a poor outcome [62].

**Spindle coma**

Spindle coma is defined as predominant theta and delta background activity with superimposed, frequent, paroxysmal spindle-shaped bursts. The spindles are usually bilateral, symmetric, synchronous, and have frequencies of up to 14 Hz (Figure 3 A). Intermittent elements of sleep architecture (i.e., K-complexes, vertex waves or slowing) may be triggered by external noxious stimuli [67, 68].

While spindle coma pattern is mainly seen in patients with injury to the pontomesencephalic junction below the thalamus [34, 56], it may also follow hypoxic-ischemic brain damage [68], traumatic brain injury [34, 69, 70], intracerebral hemorrhage [34], post-ictal states [71], intoxication [35, 36], encephalitis [37, 38], and other diffuse cerebral insults [67]. This is why the prognosis largely depends on the underlying cause. Overall, preserved background reactivity to noxious stimuli and lack of evidence of severe intracerebral, parenchymal lesions or signs of hypoxic-ischemic brain injury is associated with good prognosis [72].

**Burst-suppression**

Burst-suppression patterns are generalized, synchronous bursts of high-voltage, irregular activity and/or epileptic elements of different frequencies (e.g., such as spikes, sharp waves) that interrupt EEG suppression (Figure 3 B). Both bursts and periods of suppression may vary in duration. With deeper coma, the proportion of bursts decreases while suppression increases and sometimes persists without interruption [54].

Hypoxic-ischemic encephalopathy, intoxication with sedative drugs, anesthetics, and hypothermia are the major underlying etiologies that determine outcome [62, 73 - 77]. It remains unclear whether a reactive burst-suppression pattern to external stimuli (i.e., an interruption by stimulation) is predictive of better outcome.

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![Figure 3: Electroencephalographic patterns in coma (part 2). A spindle coma pattern; B burst-suppression; C low-voltage delta coma; D electro-cerebral inactivity](image-url)
Low-voltage delta coma

This coma pattern consists of persistent theta and delta activity with small amplitude (usually < 20 µV; Figure 3 C) [62]. This low-voltage activity may also be present in healthy individuals but usually with preserved background reactivity to external stimulation and intrusions of alpha and beta activity. A low-voltage, slow and unreactive EEG pattern is associated with large and severe brain damage (i.e., hypoxic-ischemic encephalopathy and severe traumatic brain injury) [56, 64, 78], and poor outcome.

Electro-cerebral inactivity

Electro-cerebral inactivity, also described as isoelectric, nonreactive EEG, flat EEG or electro-cerebral silence, is the expression of severe and widespread cerebral dysfunction in which EEG activity is undetectable (i.e., amplitudes of < 2 µV) with conventional scalp electrodes placed at double the routine international 10-20 electrode distances with body core temperature above 34 degrees centigrade, and with at least 30 minutes of continuous recording (Figure 3 D). Artifacts from electrocardiograph, respiration, and intravenous drips must be differentiated from brain activity and the term should only be used in the global absence of electrical activity, even after intense sensory stimulation [54]. In addition, marked hypothermia must be excluded, as it may result in potentially reversible electro-cerebral inactivity. Most common etiologies are diffuse hypoxic-ischemic brain injury and severe intoxication with nervous system depressant drugs. As the clinical impact of electro-cerebral inactivity is grave, the standard protocols for obtaining "brain death" recordings must be followed, such as proposed by the American Clinical Neurophysiology Society [79]; of note, however, a brain death diagnosis does not require EEG in Switzerland. Patients with electro-cerebral inactivity on the EEG either die or remain in a persistent vegetative state [54, 79].

Periodic EEG coma patterns

Aside from changes in background activity in coma, periodic patterns are also frequently seen with altered mental status. Such recurring EEG elements usually consist of waves or complexes that repeat with a variety of intervals, ranging from 0.3 to several seconds, and which occupy most of at least a 20 minute standard recording. Different types of periodic discharges have been described, such as periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BIPLEDs), generalized periodic epileptiform discharges (GPEDs) [80]. Among different metabolic and toxic derangements, periodic patterns in coma are mostly seen in patients with hypoxic-ischemic insult, nervous system infections, and multi-focal brain trauma.

Periodic non-epileptic patterns are often difficult to differentiate from clinical states of coma with EEG ictal activity. The latter consist of complexes of spike, spike waves, or sharp waves. In these states of nonconvulsive status epilepticus, the periodic epileptic discharges usually occur at higher frequencies. In addition, there are often subtle clinical correlates, such as facial, periocular, eyelid, and limb myoclonias, staring or rigidity [81]. With ongoing seizure activity, the interposed background activity may slow down and not be identified as the frequency of epileptic discharges increases.

Conclusion

The EEG provides objective electrophysiological measurements of cerebral dysfunction, and complements clinical and neuroimaging assessment of comatose patients. Aside from the detection of epileptic activity seen in subclinical seizures or occult status epilepticus, EEG frequency, amplitude and distribution patterns may indicate diffuse, cortical, subcortical or arousal dysfunction. EEG patterns and background reactivity may provide information on prognosis and may suggest specific causes for coma.

Conflicts of interest

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References

31. Molofsky WJ. Alpha coma in a child. J Neurol Neurosurg Psychiatry 1982; 45: 95
34. Synet VM, Glasgow GL. Recovery from alpha coma after depression sickness complicated by spinal cord lesions at cervical and midthoracic levels. Electroencephalogr Clin Neurophysiol 1985; 60: 417-419
35. de Boer WB, Kendall PA, Breheny FX. Alpha coma and barbiturate poisoning. Anaeth Intensive Care 1989; 17: 503-504
59. Wennervirta JE, Ermes MJ, Tiainen SM et al. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quan-


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