EEG and Epilepsy

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Electroencephalogram (EEG)

- **electro** = electrical; **encephalo** = brain; **gram(ma)** = picture
- Electroencephalograph
- Electroencephalography
- Brain waves
First EEG

- Hans Berger in 1924 (Berger, 1929).
- He used two large sheets of tinfoil which served as electrodes, one on the forehead and one on the back of the head.
- 1929: First paper on human EEG.
Pathophysiology

Synaptic transmission

Action potential
Electroencephalogram (EEG) is a recording of the dendritic potentials in the upper cortical layers as they appear in the scalp.

- EEG is state dependent.
- EEG changes with age, arousal level, sleep stage, cerebral dysfunction, etc.
- Pacemaker: thalamus.
Electrode placement -
International 10-20 system

- Jasper (MNI), Schwab & Abbott (MGH), Gibbs (CUH), Cobb (National Hosp for Neuro Disorders)
- 1958: International Federation of Societies of EEG and Clinical Neurophysiology 發表 10-20 system
International 10-20 system
<table>
<thead>
<tr>
<th></th>
<th>International 10-20 system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fp</td>
<td>frontopolar or prefrontal (額前葉)</td>
</tr>
<tr>
<td>F</td>
<td>frontal (額葉)</td>
</tr>
<tr>
<td>C</td>
<td>central (額葉中心溝)</td>
</tr>
<tr>
<td>T</td>
<td>temporal (顳葉)</td>
</tr>
<tr>
<td>P</td>
<td>parietal (頂葉)</td>
</tr>
<tr>
<td>O</td>
<td>occipital (枕葉)</td>
</tr>
<tr>
<td>A</td>
<td>ear or mastoid</td>
</tr>
<tr>
<td></td>
<td>單號代表左側</td>
</tr>
<tr>
<td></td>
<td>F3 = left mid-frontal</td>
</tr>
<tr>
<td></td>
<td>P3 = left parietal</td>
</tr>
<tr>
<td></td>
<td>雙號代表右側</td>
</tr>
<tr>
<td></td>
<td>T4 = right temporal</td>
</tr>
<tr>
<td></td>
<td>A1 = right ear</td>
</tr>
<tr>
<td></td>
<td>Z (zero) 代表中線</td>
</tr>
<tr>
<td></td>
<td>Cz = vertex</td>
</tr>
</tbody>
</table>
Applications of EEG

- As a diagnostic tool
  - Cerebral function vs structural abnormalities.
  - Principal applications: epilepsy, head trauma and coma, anoxia, intoxications and cerebral infections.
  - Reflects general pathophysiological processes.
  - Little specificity for particular diseases.

- As a monitoring tool
  - The progression (or remission) of brain dysfunction and in their therapeutic/pharmacologic management.

- As a research tool
  - Computer driven powerful analyses of EEG patterns in schizophrenia research, personality studies, etc.
Normal EEG rhythms

- **Alpha: 8 to 13-Hz**
  - 85% of adults 9.5-10.5 Hz
  - occipital region
  - relaxed with eyes closed

- **Theta: 4 to 8-Hz**
  - <15µV (10% in the 15-25µV range)
  - temporal prominent during sleep

- **Beta: 14 to 30-Hz**
  - 5-20 µV
  - frontal/central maximum
  - increased by tranquilizers & tense

- **Delta: 0.5 to 4-Hz**
  - stage 3-4 sleep (slow-wave sleep)
  - pathological in the normal waking adult
Staging of sleep

- Stage W = wakefulness
- Stage 1 (drowsiness): suppression, low amp theta + alpha (<50%), slow EM
- Stage 2 (light sleep): theta, V-waves, sleep spindles, K complexes, POSTS
- Stage 3 (moderate sleep): + 20-60% delta >75 µV
- Stage 4 (deep sleep): > 60% delta >75 µV
- Stage REM: low amp theta + alpha + beta, more EM, less submental EMG, ↑ BR, ↓ peristalsis, erection
**EEG abnormalities**

- **Slowing**
  - Generalized: metabolic
  - Focal: lesion

- **Epileptiform**
  - Spikes
  - Spike-and-waves
  - Paroxysmal rhythmic

- **Periodic**

- **Asymmetry**

- **Non-reactive**

- Physiologic activity (-)
Seizure

- Seizure -- isolated, nonrecurrent attack.
- Paroxysmal alteration of behavior, movement, or sensation.
- Synonym -- fit, attack, turn, blackout
- Epileptic seizure
- Non-epileptic seizure
Epilepsy

- Epilepsy -- a condition characterized by recurrent epileptic seizures unprovoked by any immediately identifiable cause.
- Epileptic seizure -- a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain.

Commission on Epidemiology & Prognosis of the ILAE (1993)
Classification of epileptic seizures

- Idiopathic, primary -- the seizures may be the only sign of brain abnormality and it is impossible to ascertain the nature of the disease
- Symptomatic, secondary -- the seizures have an identifiable and acquired structural cause

I. Partial, or focal, seizures - seizures beginning locally
II. Generalized seizures
   - bilaterally symmetrical & without local onset
III. Unclassified epileptic syndromes
IV. Prolonged or repetitive seizures
   - status epilepticus

ILAE, 1981
Proportion of seizure types

- GTCS: 23%
- CPS: 36%
- SPS: 14%
- Absence: 6%
- Myoclonic: 3%
- Other Gen: 8%
- Unclassified: 3%
- Unknown: 7%

Rochester, Minnesota, 1935-1984
Incidence & Prevalence

- **Incidence**: # of new cases within a population in a specific period of time.
  
  \[ \frac{70}{100,000} \]

- **Prevalence**: ratio of people affected to those not affected at a given time
  
  - 10% at least 1 seizure in a lifetime
  - **Active epilepsy**: 5-10/1000
Proportion of epilepsy by etiology

- Idiopathic: 65%
- Rochester, Minnesota, 1935-1984
Proportion of etiology within age groups

Rochester, Minnesota, 1935-1984
Diagnosis of epilepsy

- Clinical picture
  - Clinical history
  - Description of Sz
  - Symptomatology
  - Physical/Neurologic examination

- EEG
  - Background activity
  - Epileptiform activity
    - Interictal
    - Ictal
    - Postictal

- Laboratory tests
- Neuroimaging
Background activity

- Primary epilepsy
  - Normal background
  - No structural lesion
  - Genetic trait
- Cryptogenic epilepsy
  - Slow background
  - No structural lesion

- Symptomatic epilepsy
  - Slow background
    - diffuse encephalopathy
    - focal encephalopathy
  - Structural lesion
Epileptiform discharges

- Spikes (40-80 ms)
- Sharp waves (80-200 ms)
- Spike-wave complexes
  - Repetitive >3 s
  - Typical : 2.5-3.5 Hz
  - Atypical : <2.5 or >3.5 Hz
- Polyspikes
  - > 3 repetitive spikes
  - > 10 Hz
- Polyspike-waves
- Paroxysmal rhythmic waves
Partial seizures

- **Motor**
  - Tonic, clonic, grimacing
  - Versive, adressive
  - Posturing
    - Fencing, bowing
  - Postictal todd’s paralysis

- **Sensory**
  - Tingling, numbness
  - Vertiginous
  - Odd mental and emotional events, such as déjà vu
  - Hallucinations
    - Auditory, visual
Simple partial sz

- No loss of consciousness
- Signs and symptoms:
  - convulsive jerking, tingling, scintillation, sweating, dilation of pupils, *déjà vu*
  - Jacksonian march: tingling and jerking may begin in one part of the body and spread to various parts of the body

- Hallucinations
  - Simple
  - Complex (formed)

- Autonomic
  - Gustatory (taste)
  - Epigastric fullness
  - Nausea
  - Sweating
  - Flushing
  - Pallor
Complex partial sz

- With impaired consciousness
- >50% seizures in adults are CPS
- 80% temporal lobe
- 20% frontal lobe
- Aura → motionless stare → automatisms
  (chewing, smacking) → 2nd GTCS
Automatisms

- Oro-alimentary
  - chewing, smacking, swallowing, drooling
- Mimicry
  - fear, laughter, anger, excitement
- Gestural
  - tapping, patting, rubbing, fumbling
- Ambulatory
  - Walking, circling, running
- Verbal
  - humming, whistling, grunting, phrasing
- Responsive
  - quasi-purposeful behavior
Benign focal epilepsy of childhood

Benign rolandic epilepsy & Benign occipital epilepsy

**Clinical criteria**
- No brain damage
- Family history of idiopathic epilepsy (+)
- Onset between 1.5-13 yr
- Tonic/atonic seizures (-)
- Remission before 20
- No behavioral or cognitive impairment

**EEG criteria**
- Normal background
- Normal sleep patterns
- Interictal focal sharp waves
- Possible multifocal sharp waves
- Possible brief bursts of generalized spike waves
- Increased focal sharp during slow sleep
Benign rolandic epilepsy

- 15% of all childhood epilepsy
- Onset: 3-13 (5-10) y/o
- Partial sz with 2nd GTCS (2/3)
- Usually occur during sleep
- Sz usually infrequent

- Normal intelligence
- No neurological abnormality
- Family history 10-60%
- Autosomal dominant
- EEG: centro-temporal spikes
- Disappear < 15 y/o
Absence

- **Typical absence**
  - Simple absence 9%
  - Clonic component 45%
  - Decreased tone 22%
  - Increased tone 4%
  - Automatism 63%

- **Atypical absence**
  - Onset and end not abrupt
  - Mental retardation
  - More tone changes
  - EEG: < 2 or > 4 Hz S-W-C

- **Typical absence**
  - "Petit mal"
  - Onset 3-12 (4-8), F>M
  - Brief interruption of consciousness
  - Simple automatisms:
    - Smacking, blinking
  - GTCS 40%
  - Abrupt onset and end
  - Provoked by HV or photic stimulation
  - Neurologically normal
  - EEG: 2-4 Hz S-W-C
  - Usually cease by age 20
GTCS

- Loss of consciousness
- **Tonic phase**
  - 10-30 seconds
- **Clonic phase**
  - 30-60 seconds
- **Postictal phase**
  - 2-30 minutes

- Sudden onset, gradual recovery
- Epileptic cry, cyanosis, upward gaze, tongue-bite, salivation, sphincter incontinence
- An aura indicates a partial onset
- Common in non-REM sleep
Generalized seizures

- **Tonic seizures**
  - begin in childhood
  - associated with other epileptic syndromes
  - last less than a minute
  - violent spasm or stiffening;
  - flexed upper extremities & extended lower extremities

- **Clonic seizures**
  - common in neonates/children,
  - slow repetitive muscular jerks
  - seconds to minutes

- **Atonic seizures**
  - sudden loss of postural tone
  - falls with high risk of injury
  - regains full consciousness within minutes
  - often with other sz types
  - common in Lennox-Gastaut syndrome

- **Myoclonic Seizures**
  - single or multiple irregular, involuntary contractions of muscles
Comparison of different kinds of epilepsy

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Usual duration</th>
<th>Loss of consciousness</th>
<th>Postseizure confusion</th>
<th>EEG during seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple partial</td>
<td>5-10 s</td>
<td>No</td>
<td>No</td>
<td>Normal or focal spikes</td>
</tr>
<tr>
<td>Complex partial</td>
<td>Variable: 5-10 s;</td>
<td>Yes</td>
<td>Yes</td>
<td>Focal activity spreading to involve one or both hemispheres</td>
</tr>
<tr>
<td></td>
<td>1-2 min; &gt;/= 5 min (rarely)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>5-10 s; may cluster</td>
<td>Yes</td>
<td>No</td>
<td>Generalized, 3/s, spike and wave</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>1-2 min</td>
<td>Yes</td>
<td>Yes</td>
<td>Series of generalized, high-amplitude spikes</td>
</tr>
</tbody>
</table>
Juvenile myoclonic epilepsy

- 5-10% of epilepsy cases
- Polygenic inheritance
- Onset: 13-19 y/o
- 3 sz types:
  - Typical absence
  - Myoclonic jerks
  - GTCS

- Sleep deprivation, alcohol, flash lights (photosensitive)
- EEG: generalized 4-6 Hz ~20 s polyspike and slow waves
- VPA → 90% sz-free
- High relapse rate
Infantile spasms

- 0.14-0.19/1000 (0-9 y/o)
- Family history: 7-17%
- Onset: 4-8 months of age
- “Salaam attacks”, in clusters
- EEG: hypsarrhythmia

- ACTH, VGB → 60% remit
- 70-90% mental retardation
- 35-60% → chronic epilepsy
- 5% complete recovery
Lennox-Gastaut syndrome

- Onset: 4 m/o to 14 y/o
- Multiple sz types: myoclonic, atypical absence, tonic, atonic, GTCS
- Mental retardation
- Status epilepticus
- EEG:
  - Bilateral asymmetric 1-2.5 Hz spike-wave complex + abnormal background + generalized rhythmic fast spikes during sleep

- Etiologies (Ohtahara 1988)
  - Cryptogenic 26%
  - Cerebral lesions 12%
  - Cerebral palsy 28%
  - Postencephalitic 12%
  - West syndrome 8%
  - Tuberous sclerosis 4%
  - Others 10%

- Poor prognosis
- Totally dependent
Febrile convulsion (熱痙攣)

- 2-5% of all children
- Age of onset: 3M-5Y (Peak: 2-4Y)
- Usually at onset of fever
- Generalized T-C sz
- Recur in 30-50%

Complex FC
- Duration > 30 min.
- Focal sz
- Todd’s paralysis
- Recurs <24 hr

Risk of developing chronic epilepsy
- Onset < 13M
- Prior neurological abnormalities
- Complex FC
Non-epileptic seizures

- Neurological
  - Migraine
  - Movement disorders
  - Vestibular disorders
  - TIAs
  - Tonic spasms of CVA/MS
  - Sleep disorders
- Malingering/factitious
- Psychological/psychiatric
- Psychogenic seizures

- Metabolic
  - Hypoglycemia
  - Hypocalcemia
  - Drug used or abuse
  - Acute encephalopathy
- Cardiopulmonary
  - Vasovagal syncope
  - Micturition syncope
  - Arrhythmia
  - Outflow obstruction
  - Pulmonary hypertension
Pseudoseizures

- 5-20% of OPD epileptics
- 20-30% of uncontrolled epileptic patients
- 20-30% also have epilepsy
- F : M = 3-4 : 1
- 83% are 15-35 y/o
- Gradual onset of attack
- Prolonged unresponsive
- Head side to side
- Pelvis thrusting

- Generalized movement with preserved consciousness
- Occur in company
- Prolonged attacks
- Usually no incontinency, tongue-bite or injury
- Normal EEG
- Unresponsive to AEDs
- Poor psychosocial hx
- Emotional related
Evaluation of epilepsy

- Clinical history
  - Patient, care-giver, medical record
- EEG
  - Routine + sleep + special electrodes
  - Video-EEG monitoring
  - MEG, Deblurred data
- Neuroimaging
  - CT, MRI, MRS, SPECT, PET
- Others
  - Neuropsychological assessment
Neuroimaging necessary (MRI/CT)

- All cases of partial epilepsy
- Neonatal onset seizures
- Seizure onset after 20 years
- Generalized seizures not responsive to medication
- Presence of focal neurological signs
Management of GTCS

- Loosen clothing around the person's neck
- Remove glasses, protect the person's head
- Place a cushion or pillow under the person's head
- Turn the person on his side to keep the airway clear
- Do not try to restrain or put anything in the mouth
- Do not offer anything to drink until completely awake
- Never move the person while the seizure is in progress
- Call an ambulance if
  - Convulsion > 5 min.
  - Cluster seizures
  - First seizure
Initiation of treatment - Definitely

**With structural lesion**
- Brain tumor (meningioma, glioma, neoplastic tumor)
- Arteriovenous malformation (AVM)
- Infection (abscess, herpes simplex encephalitis)

***EEG, MRI & Neurological examination needed

**Without structural lesion**
- Epilepsy in sibling
- EEG with definite epileptic pattern (JME, LGS)
- History of prior acute sz
- History of brain injury or stroke, central nervous system infection, or significant head trauma
- Todd's paralysis
- Status epilepticus at onset
Treatment of epilepsy

- Medical treatment
  - Western medicine
  - Herbal medicine
- Epilepsy surgery
- Vagus nerve stimulation
- Ketogenic diet
- Biofeedback
- Traditional
- Religious
## Choice of AEDs

<table>
<thead>
<tr>
<th>Seizure pattern</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>CBZ, VPA</td>
<td>GVG, PHT, LTG, CLB, GBP, AXM, FBM, PB</td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd generalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic</td>
<td>VPA, CBZ</td>
<td>PHT, LTG, CLB, GVG, PB, AXM, FBM</td>
</tr>
<tr>
<td>Tonic / Clonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>ESM, VPA</td>
<td>LTG, CZP, AXM</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>VPA</td>
<td>LTG, CLB, CZP, AXM, PB, FBM, CBZ, PHT, GBP</td>
</tr>
<tr>
<td>Atonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonic</td>
<td>VPA</td>
<td>CZP, PCT, PB, AXM</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>ACTH</td>
<td>GVG, NZP, CZP</td>
</tr>
</tbody>
</table>

CBZ=carbamazepine, VPA=valproate, ESM=ethosuximide, GVG=vigabatrin, PHT=phenytoin, LTG=lamotrigine, CLB=clobazam, GBP=gabapentin, AXM=acetazolamide, FBM=febamate, PB=phenobarbitone, CZP=clonazepam, PCT=piracetam, NZP=nitrazepam
Adverse effects of AEDs

- Skin rash, alopecia, coarse skin, edema
- Blood, hepatic, renal dysfunction
- Dizziness, vertigo, diplopia, unsteady gait, ataxia, tremor
- Drowsiness, inattention, slow reaction, poor memory and learning
- Asthenia, body weight gain/loss
- Psychosis, personality and behavioral changes
Factors of lowering seizure threshold

- Deprived sleep
- Exhaustion
- Physical illness
- Menstruation
- A-V stimulation
- Fasting

- Emotional stress
- Excitement
- Depression
- Caffeinated drinks
- Alcohol
- Sedatives
Indicators of poor prognosis

- Poor compliance
- Incorrect diagnosis or classification
- Inappropriate AED or dosage
- Interaction of polytherapy
- Partial seizures, multiple seizure types
  - CPS, EPC, West syndrome, L-G syndrome, PME, JME

- Long history and frequent seizures
- Neonatal onset
- Structural brain lesion, focal deficit
- Mental retardation, chronic psychosis
- Abnormal EEG (background, paroxysms)
When to stop AEDs

- Seizure-free period:
  - Children: 2 years
  - Adults: 2-4 years

- Seizure types

- Willingness of the patient

- Appropriate timing of withdrawal
Living with epilepsy

- **Teratogenicity:**
  - Normal population: 2-3%
  - Epileptic women not taking AED: 3-4%
  - Epileptic women taking 1 AED: 6-7%
  - Epileptic women taking >1 AEDs: >10%

- Some AEDs can lead to failures of oral birth control pills
  - Seizures may be more frequent during pregnancy, and harm both the baby and the mother
  - AED in breast milk is usually too low to harm the child

- Occupations not appropriate for people with epilepsy
  - Should a seizure occur may endanger the life of others, e.g. occupations in the military, airlines, and fire brigade, professional drivers, pilot, surgeons, etc
Epilepsy surgery

- Resective surgery
  - Temporal lobectomy
  - Focal cortical excision
  - Hemispherectomy
  - Stereotactic cauterization

- Disconnective surgery
  - Corpus callosotomy
  - Multiple subpial transection
Vagus nerve stimulation

- 1938 Animal studies
- 1988-2000 Human trials
  - >3000 patients
  - Effective
  - Mild adverse effects
- Mechanism
  - Vagus nerve → solitary tract → hippocampus, amygdala, hypothalamus, insula cortex, dorsal raphe
Vagus nerve stimulation

- Safe
  - Minor operation
  - Mild adverse effects duration stimulation
  - No drug interactions
  - No adverse effects on cognitive function

- Effective
- Improves quality of life
- High acceptance (94% after 1 year)
- Expensive
Treatment of epilepsy

1. Single antiepileptic drug
   - 30% difficult to control
   - 70% well controlled

2. Two antiepileptic drugs
   - 25% difficult to control
   - 5% well controlled

3. Three antiepileptic drugs
   - 20% difficult to control
   - 5% well controlled

- 10% surgery
  - 30% difficult to control
  - 70% well controlled

Trial new drugs
- 10% difficult to control
- 3% well controlled

VNS
- 7% difficult to control
- 3% well controlled
Status epilepticus - Definition

- 30 minutes of continuous seizures or lack of recovery between discrete seizure for focal, complex partial, absence and other form of convulsive seizure
- 5 minutes of continuous convulsive seizures
- 3 discrete convulsions within an hour

Mechanism of SE

- Failure of the mechanisms that terminate individual seizures (postictal refractory period).
  - neural circuits
  - excitation/inhibition balance
  - potassium channel
  - genetic
Types of SE

- Generalized convulsive status epilepticus (GCSE)
- Non-convulsive status
  - Absence or Petit mal status (spike-wave stupor)
  - Complex partial status (CPSE, psychomotor status)
- Epilepsia partialis continua (EPC)
- Myoclonic status (MSE)
  - Primary MSE (childhood & juvenile absence, JME, etc)
  - Secondary MSE (Lennox-Gastaut syndrome, myoclonic absence)
- Subtle status
## Estimated annual incidence of SE

<table>
<thead>
<tr>
<th>Seizure types</th>
<th>General population of 1,000,000</th>
<th>Taiwan population (23,000,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed epilepsies, presenting with convulsive SE</td>
<td>80</td>
<td>1840</td>
</tr>
<tr>
<td>Established epilepsy, convulsive SE</td>
<td>40-80</td>
<td>920-1840</td>
</tr>
<tr>
<td>Febrile SE</td>
<td>20-40</td>
<td>460-920</td>
</tr>
<tr>
<td>Acute symptomatic seizures</td>
<td>40-80</td>
<td>920-1840</td>
</tr>
<tr>
<td>Typical absence SE</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Complex partial SE</td>
<td>35</td>
<td>805</td>
</tr>
<tr>
<td>Neonatal SE</td>
<td>120</td>
<td>2760</td>
</tr>
<tr>
<td>Nonconvulsive SE in the mentally handicapped</td>
<td>100-200</td>
<td>2300-4600</td>
</tr>
<tr>
<td>Other SE syndromes</td>
<td>5-10</td>
<td>115-230</td>
</tr>
<tr>
<td>Total # of SE per annum</td>
<td>441-646</td>
<td>10143-14858</td>
</tr>
<tr>
<td>Total # of convulsive SE per annum</td>
<td>180-280</td>
<td>4140-6440</td>
</tr>
</tbody>
</table>
Acute physiologic changes - Systemic

- Hypertension → hypotension, arrhythmia
- Hypoxia & Acidosis
- Hypoglycemia
- Hyperkalemia
- Rhabdomyolysis → myoglobinuria → acute tubular necrosis → renal failure
- ↑ Catecholamine → Leukocytosis
- Hyperthermia - 83% core temperature → 42°C
- Respiratory function: ↑ intravascular pressure (pulmonary capillaries) → pulmonary edema
Management of SE - Premonitory stage (0-10 min.)

- Avoid hypoxia
- Set up intravenous line
- Examine patient
- Monitor patient
- Detailed history taking
- Establish etiology
- Seek specialist help
Status epilepticus

- SE is a life-threatening neurologic disorder.
- If sustained for > 60 minutes → profound systemic and neuronal damage.
- Overall mortality 15-20%.
- If sustained > 4-12 hours. → mortality 50-80%.
- Effective treatment may lower the mortality.
- Should be treated as a medical emergency.