Coma and related disorders of consciousness

Pathophysiology:
Normal consciousness requires the intact functioning of:

- Brainstem (esp reticular formation)
- Thalamus
- Hypothalamus
- Cortex

A ‘conscious’ state depends on intact cerebral hemispheres interacting with the ascending reticular activating system (RAS) in the brainstem, hypothalamus and thalamus. Lesions diffusely affecting the cerebral hemispheres, or directly affecting the reticular activating system cause impairment of consciousness.

Neuronal groups within the brain that utilize dopamine, norepinephrine and serotonin provide diffuse modulatory systems that ascend in the brainstem and establish the general state of awareness of the brain.

Noradrenergic fibres from the *locus coeruleus* distribute norepinephrine throughout the brain, including the cortex, cerebellum, thalamus and spinal cord. There are few individual neurons, but each branch widely. A single locus coeruleus neuron makes as many as 250,000 synapses that spread from cerebral cortex to cerebellum.

Serotonergic neurons located in the *raphe nuclei* near the midline of the brainstem innervate most of the brain in a manner similar to the locus coeruleus. Projections from the locus coeruleus and raphe nuclei together form the reticular activating system (RAS), which serves to alert the brain to incoming sensory stimuli and to maintain the awake, interactive state. Stimulation of the RAS elicits arousal, and lesions in the RAS result in coma.

Neuropathological data suggest that three regions are involved in regulating attention: the prefrontal cortex, the posterior parietal cortex, and the thalamus. The RAS primes the cortex for stimulus reception, whereas the cortex controls and focuses this arousal energy for attention. The thalamus may serve to screen sensory input from the RAS. Lesions of these structures tend to result in disturbances of attention (delirium), rather than coma.

Two basic types of lesions result in disordered consciousness:

**Morphological (structural)**
- lesions of the upper brainstem or diencephalon
- hemispheric – interrupting flow of signals to RAS

**Metabolic**
- eg hypoglycemia resulting in suppression of neuronal activity in RAS and cortical neurons.

**Definitions**:

**Normal consciousness**: State of awareness of self and of the environment. The individual is fully awake and indicates by his speech and behaviour the same sense of awareness as that of the examiner.

**Confusion**: Inability to think with customary speed and clarity. The patient does not take into account all the elements of his/her immediate environment.

**Drowsiness**: An inability to sustain a wakeful state without external stimuli.

**Stupor**: Patient can only be aroused by vigorous and repeated stimuli.

**Coma**: The patient appears asleep but cannot be aroused by external stimuli or inner needs. There are variations in the degree of coma; in the deepest stages, no reaction of any kind is obtainable: corneal, pupillary, pharyngeal, tendon, and plantar reflexes are all absent. With lesser degrees of coma, pupillary reactions, reflex ocular movements and other brainstem reflexes are preserved.

**Classification and differential diagnosis of coma:**

Diseases that cause **no focal or lateralising neurological signs** and have a **normal cerebrospinal fluid (CSF)**.

- Drug intoxications: alcohol, opiates, benzodiazapines
- Metabolic derangements: diabetic ketoacidosis, uremia, hepatic failure
- Severe systemic infections: malaria
- Post ictal states
- Circulatory collapse: hypovolemic, myocardial infarction
- Hypertensive encephalopathy
- Hyo or hypothermia
- Endocrine: diabetes, adrenal crisis (Addisons disease).
Diseases that cause **meningeal irritation without focal or lateralising neurological signs**:

- Subarachnoid haemorrhage
- Bacterial meningitis
- Viral encephalitis

Diseases that cause **focal or lateralising neurological signs** and have **normal CSF**:

- Cerebral infarct with oedema and ‘shift’ - hemispheric or brainstem
- Epidural or subdural haemorrhage
- Brain tumours: primary – astrocytomas

**Clinical Approach**

Coma is not a disease per se, but rather a *symptom* of an underlying disease. Questioning relatives, friends, or the ambulance team, followed by a general and neurological examination all provide important diagnostic information:

**History**

Possible cause of impaired level of Consciousness:

- Head injury leading to admission: Diffuse axonal injury or intracranial hematoma.
- Previous head injury (eg 6 weeks): Chronic subdural hematoma
- Sudden Collapse: Subarachnoid haemorrhage, Intracerebral Haemorrhage
- Limb twitching, incontinence: Epilepsy
- Gradual development of symptoms: Mass lesion, metabolic or infective cause

**General examination**

The patient’s lack of co-operation should not limit the general exam as this may reveal important diagnostic information:

The presence of:

- Lacerations, bruising, CSF leaks may indicate: head injury
Tongue biting and urinary incontinence may indicate: epilepsy

Infective source (ears, sinus, lungs) may indicate: cerebral abscess

Also note the smell of alcohol and the presence of needle marks.

**Neurological Examination**

Accurate assessment of the level of consciousness is essential to determine deterioration or improvement in a patient’s condition. In 1974, Teasdale and Jennet, in Glasgow, developed a system for conscious level assessment. They discarded vague terms such as stupor, semicoma, deep coma and described conscious level in terms of

- **EYE opening**
- **VERBAL response**
- **MOTOR response**

The Glasgow Coma scale is now widely used throughout the world for serial assessment and prognosis of patients with head injuries. It is graded on an overall score of 15/15, with the minimal score possible being 3/15. Coma is defined as a score of 8 or less.

**Eye Opening:**
- Spontaneously: 4
- To speech: 3
- To pain: 2
- None: 1

**Verbal Response:**
- Orientated, knows place and time: 5
- Confused, talks in sentences but disorientated to time and place: 4
- Utters occasional words rather than complete sentences: 3
- Incomprehensible sounds, groans or grunts: 2
- No verbal response: 1

**Motor response:**
- Obey commands: 6
- Localises to pain: 5
- Withdraws to pain: 4
- Flexes in response to pain (decorticate): 3
- Extends in response to pain (decerebrate): 2
- No motor response: 1
Specific points of importance on the neurological exam:

**Eyes:**

*Pupillary reaction*: Unilateral enlargement suggests brainstem compression. Pin point pupils suggest a pontine tegmental lesion. These have such a slight constriction to light that it can only be detected with a magnifying glass.

- Drugs – opiates (heroin and morphine) cause pinpoint pupils, poisoning with atropine or atropinic drugs is characterized by widely dilated and fixed pupils.

*Ocular Movements*: are altered in a variety of ways:

A lateral and slight downward deviation of one eye suggests the presence of a third nerve palsy, and a medial deviation, a sixth nerve palsy.

There may be persistent conjugate deviation of the eyes to one side – away from the side of the paralysis with a large cerebral lesion (ie looking towards the lesion) and toward the side of the paralysis with a unilateral pontine lesion (looking away from the lesion).

Oculocephalic (doll’s eye movements) are elicited by briskly turning or tilting the head (NB provided that the presence of cervical spine fractures has been excluded). This produces conjugate movement of the eyes in the opposite direction. This response is not present in the normal alert person.

Loss of blink in response to touching the cornea (corneal reflex) is a sign of deepening coma. The afferent limb of this pathway is the trigeminal nerve, the efferent limb is both facial nerves.

*Oculovestibular or caloric responses* are elicited by irrigating the ears alternatively with cold and then hot water.

Irrigation of each ear with 10ml of cold water normally causes slow, conjugate deviation of the eyes towards the irrigated ear, followed in a few seconds by compensatory nystagmus (fast component away from the stimulated side). In comatose patients, the fast ‘corrective’ phase of the nystagmus is lost and the eyes are tonically deviated to the side irrigated with cold water, or away from the side irrigated with warm water.

**Spontaneous limb movements**

Restless movements of the limbs and variable oppositional resistance to passive movement (paratonic rigidity) suggest that the level of coma is not deep.
Seizures may suggest status epilepticus, or a focal lesion. Chorea, hemiballismus suggest a disorder of the basal ganglia. Myoclonus usually suggests a diffuse hypoxic event.

**Postural Changes**
Decerebrate posturing consists of extension and adduction of the lower limbs, internal rotation of the shoulders, and extension at the elbows and wrists. This pattern of posturing is seen with bilateral midbrain or pontine lesions, and less commonly with metabolic encephalopathies. Decorticate posturing consists of bilateral flexion of the elbow and wrists, adduction of the shoulders and extension of the lower limbs. It usually signifies that the lesion lies above the brainstem – the cerebral white matter, internal capsule or thalamus. Limb weakness can be detected by comparing the response to painful stimuli. If pain produces an asymmetric response, then limb weakness is present.

**Patterns of Breathing**
*Cheyne-Stokes respiration*: oscillates between hyper and hypoventilation, usually indicates bilateral hemispheric or diencephalic lesions, may also occur with metabolic encephalopathies.

Lesions of the lower midbrain - upper pontine tegmentum may give rise to *central neurogenic hyperventilation*. It is characterized by an increase in the rate and depth of respiration, resulting in respiratory alkalosis. It must be distinguished from hyperventilation caused by medical illnesses.

Low pontine lesions, usually due to basilar artery occlusion, can result in *apneustic breathing*. Here, a prolonged inspiratory gasp occurs, with a pause of 2-3 seconds in full inspiration.

Lesions of the lower medulla can result in *ataxic or Bitot breathing*. The rhythm of breathing is chaotic, being irregularly interrupted and each breath varying in rate and depth.

**Raised intracranial pressure**
The skull contains the brain, CSF, and blood. At normal intracranial pressures of 10-15mmHg, these three components maintain volumetric equilibrium. Increased volume of one component will elevate intracranial pressure unless the volume of the other two components decreases proportionately (Monro-Kellie doctrine). Because compensatory volumetric changes have physical and physiologic limits, the ability of the skull’s contents to maintain normal pressure can be exceeded by a change of volume that is either too fast or too great. The compensatory properties of the intracranial contents follow a pressure-volume exponential curve. Increased volume of any of the three components can
be accommodated to a certain point without a change in intracranial pressure. Once that critical volume is reached, however, additional volume increase produces an increase in intracranial pressure (ICP).

![Graph showing ICP (mmHg) vs Volume]

 Eventually further small increments in volume produce larger and larger increments in intracranial pressure.

Increase ICP exerts its deleterious effect by
- distorting and shifting the brain as pressure gradients develop
- reducing the perfusion pressure of the brain

Cerebral blood Flow = \( \frac{\text{Cerebral Perfusion Pressure (CPP)}}{\text{Cerebral vascular resistance (CVR)}} \)

CPP = Systemic BP - ICP

Under normal conditions the cerebral blood flow is coupled to energy requirements of brain tissue. Various mechanisms acting on the arterioles maintain a cerebral blood flow sufficient to meet the metabolic demands. Autoregulation is a compensatory mechanism that permits fluctuation in the cerebral perfusion pressure within certain limits without significantly altering cerebral blood flow. A drop in CPP produces vasodilatation, thereby maintaining flow, a rise in the CPP causes vasoconstriction.

![Graph showing CBF maintained despite change in CPP vs Cerebral perfusion pressure (CPP)]
Autoregulation fails when the CPP falls below 60mmHg or rises above 160mmHg. At these extremes, cerebral blood flow is more directly related to the perfusion pressure.

Common examples of a significant volumetric change in one or more of the three normal intracranial components are cerebral oedema (brain), hydrocephalus (CSF) and cerebral venous occlusion (blood).

There are different forms of cerebral oedema:
- Vasogenic – excess protein rich fluid passes through defective vessel walls to the extracellular space, especially in the white matter. This usually occurs around tumours and infective mass lesions of the brain.
- Cytotoxic – fluid accumulates within cells (neurons and glia). With ischaemic damage, as cell metabolism fails, intracellular Na⁺ and Ca²⁺ increases and the cells swell.
- Interstitial – when obstructive hydrocephalus develops, CSF is forced through to the extracellular space, especially around the periventricular white matter.

**Clinical features of raised intracranial pressure**

Headache – worse in the mornings, aggravated by coughing, stooping, sneezing.
Vomiting - occurs with an acute rise in intracranial pressure

Specific signs if raised ICP (esp if prolonged)
- Cardiovascular – Blood pressure elevation accompanied bradycardia and respiratory slowing. This may be due to direct medullary compression.
  This “Cushing response” is a late sign of increased ICP.
- Pulmonary – Haemorrhagic pulmonary oedema. The exact mechanism for this is unclear.
- Neurologic – Papilloedema. Increased CSF pressure in the optic nerve sheath impedes venous drainage and axonoplasmic flow in optic neurons. Swelling of the disc, and retinal and disc haemorrhages result.
  An abducens palsy (due to direct compression of the nerve) and deteriorating level of consciousness are other signs.

Specific Syndromes
Specific syndromes may appear when ICP is raised by the presence of an intracranial mass
- *Transstentorial herniation*: a laterally placed supratentorial mass may push the uncus and hippocampus medially into the tentorial hiatus. The oculomotor nerves, cerebral peduncles, cerebral aqueduct and the midbrain (containing the RAS) are vulnerable to compression from the displaced temporal lobe. The resulting clinical signs are due to compression of the above structures:
<table>
<thead>
<tr>
<th>Compressed Structure</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor nerve</td>
<td>Ipsilateral pupil dilatation, and failure to react to light</td>
</tr>
<tr>
<td>Midbrain</td>
<td>Decerebrate posturing</td>
</tr>
<tr>
<td>RAS</td>
<td>Coma</td>
</tr>
<tr>
<td>Contralateral cerebral peduncle</td>
<td>Ipsilateral hemiparesis (false localizing sign)</td>
</tr>
<tr>
<td>Cerebral aqueduct</td>
<td>Headache and vomiting due to acute hydrocephalus</td>
</tr>
</tbody>
</table>

**Central tentorial herniation**

A midline lesion or diffuse swelling of the cerebral hemispheres results in a vertical displacement of the midbrain and diencephalon through the tentorial hiatus. Damage to these structures occurs either from mechanical distortion or from ischaemia secondary to stretching of perforating vessels.

**Tonsillar herniation**

Herniation of the cerebellar tonsils into foramen magnum causes compression of the medulla. Clinical signs include deteriorating level of consciousness, nuchal rigidity and respiratory failure. An injudicious lumbar puncture in the presence of a mass lesion may create a pressure gradient sufficient to induce tonsillar herniation.

**Treatment**

Management of specific causes of increased ICP includes: Removal of intracranial masses, shunting of obstructed CSF.

**Non specific treatment**

Control of Respiration: Accumulation of CO₂ (PaCO₂ > 40mmHg) will increase cerebral blood flow and raise ICP. Maintenance of normocarbia is thus a therapeutic goal.

Control of body temperature: hypothermia reduces cerebral metabolism and lowers ICP. Hyperthermia increases ICP. Thus, fever must be controlled.

Osmotic diuretics: Mannitol or glycerine reduce ICP by establishing an osmotic gradient between the plasma and brain tissue.

Corticosteroids: Effective only in the treatment of vasogenic oedema (ie due to a large tumour). CSF drainage: In acute hydrocephalus repeated CSF shunting may reduce ICP.

**Behavioural States related to coma**

**Persistent Vegetative State**

This occurs in patients with severe head injury or who have suffered an anoxic cerebral insult. These patients are initially in a state of deep coma. After 2-3 weeks, they begin to open their eyes, at first in response to painful stimuli and
later spontaneously. The patient may blink in response to threat or to light and intermittently the eyes move from side to side and they have sleep-wake cycles. These patients however, remain totally inattentive, do not speak, and show no signs of awareness of the environment or inner need. They have no cognitive neurological function, but their vegetative functions (respiration, cardiac function) are maintained (intact RAS, but nonfunctioning cerebral cortex).

'Locked in Syndrome'
This is due, most often, to a lesion in the ventral pons (basis pontis) as a result of basilar artery occlusion. Such an infarction may spare both the somatosensory pathways and the ascending reticular formation. Consciousness is thus preserved. The lesion interrupts the corticobulbar and corticospinal pathways, depriving the patient of speech and the capacity to respond in any way, except by vertical gaze and blinking.

Akinetic Mutism
This term is applied to patients who are silent and inert as a result of bilateral lesions of anterior parts of the frontal lobes, leaving the motor and the sensory pathways intact. The patient is apathetic, mute, lacks drive or impulse to action (abulic).

Brain Death
The advent of improved intensive care facilities and more aggressive resuscitation techniques has lead to an increase in numbers of patients with irreversible brain damage in which tissue oxygenation is maintained by a persistent heartbeat and artificial ventilation. In recent years, guidelines have been formulated for establishing the diagnosis of brain death. These guidelines, when fulfilled, indicate that recovery is impossible. The tests are designed to detect failure of brainstem function, but certain preconditions must first be met.

Preconditions
1) Depressant drugs must not contribute towards the patient’s clinical state – if in doubt, allow an adequate time interval to elapse to eliminate any possible persistent drug effects.
2) The patient must not be hypothermic – ensure that core temperature is not less than 36 C.
3) Exclude severe endocrine or metabolic disturbance as a possible cause for the patient’s condition.
4) The cause of the patient’s condition must be established and must be compatible with irreversible brain damage eg severe head injury, intracerebral haemorrhage.
Clinical criteria for brain death

Coma
Absence of motor responses
Absence of pupillary response to light and pupils in midposition
Absence of corneal reflexes
Absence of gag reflex
Absence of coughing in response to tracheal suctioning
Absence of caloric responses (no eye movements occur when 50 ml of iced water are slowly injected into the external meatus)
Absence of respiratory drive at a PaCO₂ of 60mmHg (no respiratory movements are observed when the patient is disconnected from the ventilator).