



Etiology and Neuropathophysiology of Coma

Komanın Nedenleri ve Nörofizyopatolojisi

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Summary

Awareness and wakefulness require an intact connection of the neocortex with the ascending reticular formation. Any factor disrupting these pathways is likely to cause a syndrome of unconsciousness. Disorders of consciousness encompass a broad spectrum of various entities with coma being the most severe form of lack of response. Awareness and wakefulness are completely absent in coma and there is no detectable sleep-wake cycle. The etiology of coma includes a comprehensive list of conditions; unilateral mass lesions compressing the contralateral hemisphere could be responsible as well as drugs or toxins leading to diffuse bilateral cortical damage. In this article specific causes of coma will be discussed and their likely pathophysiological mechanisms outlined. (*Turkish Journal of Neurology 2012; 18:126-134*)

Key Words: Wakefulness, ascending reticular activation system, coma, brain edema, cerebral herniation syndromes

Özet

Uyanıklık ve farkındalık neokorteksin mezensefalik retiküler formasyon ve asendan projeksiyon lifleri ile sağlıklı bir bağlantıda olmasını gerektirir. Bu bağlantıyı bozan herhangi bir neden bilinç bozukluğuna yol açabilir. Bilinç bozuklukları geniş bir spektrumda yer alır ve en ağır olanı koma tablosudur. Koma sırasında hastanın uyanıklığı ile farkındalığı tamamen kayıptır ve sirkadyen ritm saptanamaz. Komanın etiyojisi oldukça kapsamlıdır; karşı tarafı basınç yolu ile etkileyen tek yanlı yapısal bir lezyon kadar, ilaç veya toksin gibi çift taraflı diffüz kortikal bozukluk yaratan etkenler de komaya neden olabilir. Bu derlemede yaygın koma nedenleri üzerinde spesifik olarak durulacak ve komaya yol açan fizyopatolojik mekanizmalar gözden geçirilecektir. (*Türk Nöroloji Dergisi 2012; 18:126-134*)

Anahtar Kelimeler: Uyanıklık, asendan retiküler aktivasyon sistemi, koma, beyin ödemi, beyin herniasyon sendromları

Introduction

The main anatomic structure responsible for wakefulness in the central nervous system (CNS) is the ascending reticular activation system (ARAS). This neural network starts at the dorsal section of the pons, continues with the mesencephalon, links at the thalamus and distributes widely to both the hemispheres. In addition, ARAS is linked with some nuclei located in the pons and mesencephalon, posterior hypothalamus and the basal forebrain (Figure 1). Communication in this network is via neurotransmitters including acetylcholine,

norepinephrine, serotonin and dopamine (1). Physical or biochemical injury to this neural network may cause impairment of consciousness. The most severe condition in the spectrum of impaired consciousness is coma. Awakefulness and awareness are completely lost in a coma patient. There are various causes, of both intracranial and systemic origin, that may result in a coma. The underlying cause of coma must be discovered in the most timely fashion possible, in order to initiate specific treatment urgently. For this purpose, a systematic approach must be adopted and potential causes of mechanism must be considered in 5 major categories (2):

1. Unilateral hemispheric mass lesions compressing the diencephalon or brain stem
2. Bilateral hemispheric lesions affecting fibres of the reticular formation and thalamo-cortical cyclus at the thalamic level
3. Infratentorial lesions compressing or damaging the reticular formation located in the brain stem
4. Diffuse lesions affecting the physiological functions of the brain
5. Psychiatric conditions mimicking coma

A table classifying the causes of coma in detail can be found below (Table 1).

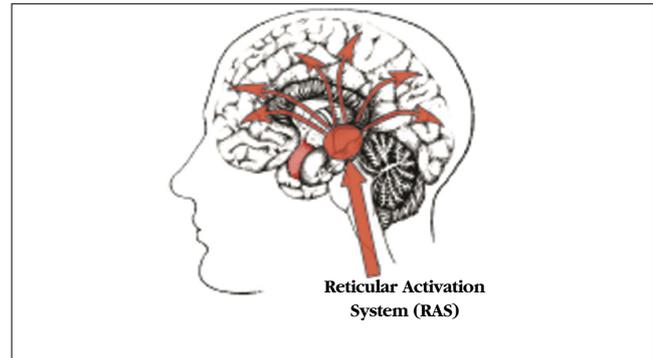


Figure 1. Reticular activation system

| Table 1. Causes of coma | | |
|--|--|---|
| STRUCTURAL CAUSES | NON-STRUCTURAL CAUSES | |
| <p>Hemispheric asymmetrical Intraparenchymal hematomas Medial cerebral artery occlusion Cerebral abscesses Brain tumours Hemorrhagic contusion Subdural hematomas</p> <p>Hemispheric symmetrical Multiple traumatic brain damage Subarachnoidal hemorrhage Bilateral anterior cerebral artery occlusion Bilateral carotid occlusion Cerebral vein thrombosis* Acute hydrocephalus Acute leucoencephalopathy* Multiple metastatic masses Cerebral gliomatosis</p> <p>Brain stem Pontine hemorrhage Basilar artery occlusion Central pontine myelinolysis Hemorrhagic contusion of the brain stem Mid brain stem tumours</p> <p>Cerebellum Cerebellar infarct Cerebellar hematomas Cerebellar abscesses Cerebellar tumours</p> | <p>Diffuse physiologic brain dysfunction Pharmaceuticals, drugs, and toxins Pharmaceuticals and drugs Sedatives Barbiturates Antidepressants Tranquillizers Salicylates Acetaminophen Anticholinergics Lithium Opiates Cocain Psychotropic drugs Amphetamines Toxins Ethyl alcohol Methanol Ethylene glucol Cyanide Carbon monoxide Lead</p> <p>Epileptic seizures</p> <p>Hypo-, hyperthermia</p> <p>Anoxia</p> <p>Malignant neuroleptic syndrome</p> <p>Endocrine – metabolic causes Hypoglycemia Hyperglycemia Hyponatremia Hypernatremia Hypercalcemia Hypocalcemia Acute uremia Hepatic encephalopathy Addison's disease Hypermagnesemia Acute hypothyroidism Thyrotoxicosis Hypercapnia</p> | <p>Infections Bacterial meningites Viral encephalitis Syphilis Sepsis Malaria Typhoid fever Subdural empyema Parainfectious encephalomyelitis</p> <p>Psychogenic causes Conversion disorder Catatonia Simulation</p> |
| <p><small>Data: Wijdicks E, The Practice of Emergency and Critical Care Neurology, 1st edition, Oxford University Press, 2010; Mumenthaler M, Mattle H, Neurologie, 12. Auflage, Georg Thieme Verlag, 2008; Posner J, Saper C, Schiff N, Plum F Diagnosis of Stupor and Coma, 4th edition, Contemporary Neurology Series, Oxford University Press, 2007</small></p> | | |

Structural causes of coma

• Hemispheric asymmetrical structural causes (unilateral hemispheric mass effect)

Unilateral structural involvement may be seen in the hemispheres as a result of hematoma, tumour, abscess or ischemia. The clinical picture results from mainly two mechanisms: direct damage in the hemispheric tissue or mass effect, i.e. displacement of the normal tissue via compression. Impaired consciousness requires diffuse injury in both hemispheres or direct involvement of the ascending reticular activation system (ARAS). Therefore, unilateral hemispheric lesions do not directly impair wakefulness, although they may cause tissue damage and they have to compress ARAS via mass effect to cause coma and stupor. Radioimaging shows the unilateral hemispheric lesion causes a midline shift in the pineal corpus; a shift of 3-5 mm, 5-8 mm, and > 8 mm may result in somnolence, stupor, and coma, respectively (3). The types and mechanisms of brain herniation resulting from the mass effect will be discussed in detail below.

• Hemispheric symmetrical structural causes (bihemispheric damage)

Bilateral structural damage in the hemispheres may impair consciousness affecting both the white matter and the cortex. Commonly seen causes include trauma related bilateral hemorrhages, metastatic masses occurring in both hemispheres, bilateral embolic infarcts or secondary to central nervous system (CNS) vasculitis, intracranial pressure increase due to subarachnoidal hemorrhage and decrease in cerebral blood flow. Bilateral carotid artery occlusion is very rare and occurs with the rapid loss of all brain functions. Spontaneous roving eye movements may appear in bihemispheric damage, as well as upward or downward deviation of the gaze; on the other hand, brain stem reflexes are usually preserved. Generalized myoclonus may be observed if there is severe cortical necrosis (2).

• Diencephalic damage

Thalamic nuclei are the most important transmitting media for data to reach the cerebral cortex. Bilateral thalamic involvement must be observed, even if rarely, for impairment of wakefulness. As the main arteries supplying blood to the thalamus branch directly from the Willis polygon, bilateral vascular involvement is commonly not seen. The only exception to this is distal basilar artery syndrome where bilateral thalamic infarct can be observed (4). Thalamic hemorrhages, local infiltrative tumours and rarely inflammatory diseases such as Behçet's disease can cause large, bilateral pathologic lesions (5). Thalamic lesions have been shown to occur frequently in patients in persistent vegetative state (6).

• Brain stem damage

Pathology studies have shown that areas extending from the caudal diencephalon do the rostral area of the pons are critical in maintaining wakefulness. Any pathology including infarcts, tumours or hemorrhages in this area, however small, may cause impairment of wakefulness. ARAS ends anatomically at the level of upper medulla and lower pons. As lesions located below the basal pons would not affect ARAS, these lesions alone would not impair wakefulness (7).

• Cerebellar mass effect

Acute cerebellar mass effect (mostly resulting from a hematoma, more rarely cerebellar infarcts or tumours) is characterized with sudden dizziness, nausea, vomiting and ataxia. Headaches usually accompany these symptoms. Most of the patients are found to have nistagmus when awake. As the condition deteriorates, consciousness is impaired as a result of upward or downward compression of the brain stem. Upward herniation usually causes the vermicular area to be displaced towards the supracellar cisterns and compress the brain stem. Patients develop a defect of wakefulness, upward gaze paresis and slowly progressing deep coma (8).

Non-structural causes of coma

• Acute metabolic or endocrine disorder

Acute metabolic disorders cause impaired consciousness, and coma rapidly, if not recognized in time. The list of metabolic causes of coma is quite long, with hyponatremia, hypoglycemia, uremia, and acute hepatic failure being the most typical. Although these disorders arising from the impairment of extracerebral systems cause hypometabolism in the brain, its exact mechanism is not yet clear. Some of the potential mechanisms are the impairment of the blood-brain barrier (BBB), direct impact of

Table 2. Some critical laboratory values that may cause coma in patients with acute metabolic or endocrine disorders

| Pathology | Serum value |
|-----------------|--------------|
| Hyponatremia | ≤ 110 mmol/L |
| Hypernatremia | ≥ 160 mmol/L |
| Hypercalcemia | ≥ 3.4 mmol/L |
| Hypermagnesemia | ≥ 5 µg /L |
| Hypercapnia | ≥ 70 mmHg |
| Hypoglycemia | ≤ 40 mg/dL |
| Hyperglycemia | ≥ 800 mg/dL |

Source: Wijdicks E, The Practice of Emergency and Critical Care Neurology, 1st edition, Oxford University Press, 2010

toxic substances including urea and ammonia, impairment of the neurotransmission axis, especially pathways where gamma aminobutyric acid (GABA) is involved (9, 10, 11). In addition to cerebral hypometabolism, cerebral edema, anoxia, accompanying epileptic seizures and ischemia resulting from cardiorespiratory resuscitation are thought to contribute to the development of coma. Symmetrical and reactive pupils, diffuse abnormal motor signs including myoclonus, tremor and asterixis, and absence focal neurologic symptoms tend to suggest coma resulting from a metabolic disorder (12, 13). Clinically metabolic encephalopathies may be similar; sometimes clinical presentation alone is not sufficient to determine etiology (14). Disorders of various levels of the neural axis occur concurrently in metabolic / endocrine coma; on the other hand, neurologic symptoms tend to be localized in coma resulting from a structural cause.

- **Diffuse physiologic brain dysfunction**

Drugs and toxins Drug intoxications and exposure to toxins are among common causes of coma. Drugs and toxins cause coma mainly through 5 mechanisms: a) causing hypoglycemia, b) causing hypoxia preventing the transport of oxygen, c) causing increase in GABA levels as a result of interaction with GABA receptors, and tendency to sleep, d) disturb wakefulness as a result of epileptic seizures, and e) drugs and toxins may cause structural damage alone or by secondary effect (2). Although various drugs and substances cause specific clinical symptoms, the physician usually encounters a complex clinical picture where multiple drugs or substances are simultaneously in effect. Some clinical presentations may be typical and recognizing the picture may be life saving. It is not possible to discuss in detail all the clinical pictures due to the drugs and substances that cause coma, but some commonly seen factors will be briefly mentioned.

Acute alcohol (ethanol) intoxication is a frequently encountered condition in the emergency room and as the cerebellar and vestibular functions are primarily affected, nistagmus, ataxia, dysarthria, and attention disorder are commonly seen while the patient is still awake. Alcoholic coma may be confused with coma from other causes (e.g., hypoglycemia, hepatic encephalopathy, subdural hematoma, bacterial meningitis) (15). Toxic alcohol derivatives including methanol and ethylene glycol may be found in products such as antifreeze or solvents. Methanol is also used in the manufacturing of illegal alcoholic beverages. Methanol rarely causes coma, and is frequently observed to cause delirium and blurred vision; however, when it does, the clinical picture is usually fatal. An important characteristic of methanol-induced coma is that impaired consciousness appears

suddenly after an approximately 12-hour latent period (16). Barbiturates are potent GABA stimulants and impair wakefulness through this pathway, causing typically a flask coma accompanying hypotension, damp skin and hypothermia (2). Tricyclic antidepressants may cause coma at a toxic dose where brain stem reflexes may be completely lost following delirium. Pupils are dilated, skin is dry and body temperature may be raised. Arrhythmias may be seen due to cardiotoxic effect and QRS complex elongation is typical (17). Overuse of benzodiazepines may create a highly flask coma, but neurologic morbidity is low and patients usually gain consciousness in 2-3 days (2). Overuse of salicylates cause metabolic acidosis, respiratory alkalosis and hypoglycemia; blood level must be > 50 mg/dL to develop coma. Patients may be agitated and hyperventilating; the clinical picture may be confused with meningococcal meningitis when hyperthermia and purpura due to platelet disorders are added (18). Acetaminophen is a common analgesic and intoxication is commonly encountered as well. This drug causes hepatic necrosis in high doses and coma occurs as a result of hepatic encephalopathy with myoclonus and asterixis. However, as the half-life of the drug varies between 4 and 120 hours depending on the level of hepatic necrosis, hepatic failure may take 4 days to develop (19). Cocaine may cause excitation through inhibition of presynaptic norepinephrine and epinephrine reuptake; hypertension, pupillary dilation and tachypnea are usually seen. Epileptic seizures are frequent, and the picture may rapidly progress to generalized tonic-clonic status. Opiates (morphine, heroin etc.) cause a flask coma with miosis and hypoventilation; light reflex may be almost impossible to obtain (20). Carbon monoxide gas is the most common cause among environmental toxins. With a 200-fold higher hemoglobin binding affinity compared to oxygen, it also rapidly impairs oxygen transfer. Carboxyhemoglobin level must be higher than 50% to develop coma. The patient may develop headache, hypotension, cardiac arrhythmias, and dyspnea before the onset of coma. Structural neurologic damage requires a toxic carbon monoxide level concurrently with hypotension; white matter is primarily affected, particularly hippocampus, cerebellum and globus pallidus (21, 22).

Epileptic seizures The causes of epileptic seizures are recurring neuron discharges. The metabolic requirements of the brain, including blood flow, increase 200-300% during the discharge and systemic hypertension occurs (23). Recurring seizures result in the impairment of the blood-brain barrier. When the metabolic requirements of the brain cannot be obtained or when the blood flow is not adequate, the endogenous reserve is used up initially,

and in case of inadequacy hypoxic ischemic neuronal damage develops and defects in wakefulness can be seen in the postictal period. Although the level of postictal consciousness disorder may vary between stupor and deep coma, postictal coma is not expected to last longer than 15-30 minutes. If it does, the following should be considered: a) The patient is in status epilepticus, where seizures are so frequent that the patient cannot regain consciousness. Status epilepticus is a medical emergency and may cause irreversible brain damage or death if untreated. Not to be omitted is nonconvulsive status epilepticus suggested by conditions where seizure history with a clear motor component is not available. Rarely in elderly patients de novo absence status epilepticus may be the underlying cause of coma unknown origin (24). However, it should also be noted that persistent epileptiform electroencephalogram (EEG) pattern can be observed prior to brain death in coma of severe metabolic or anoxic etiology (25). b) The senile changes in elderly patients (who usually also have clinical dementia) cannot handle the metabolic burden of epileptic seizures and the coma period following the seizures may extend to a few hours, frequently transforming into delirium. c) Loss of consciousness may result from a primary metabolic or primary structural pathology. The underlying cause may both cause an epileptic seizure and a defect in wakefulness (2).

Hypothermia – Hyperthermia Hypothermia may accompany some metabolic disorders (e.g., hypoglycemia), alcohol intake or drug intoxications (e.g., barbiturates). Patients are usually awake as long as the body temperature is not below 32.2°C; clinical picture varies between stupor and coma when it falls below 28°C. In temperatures below this pupils are nonresponsive and EEG tracing is an isoelectric line. The body stops shivering below 30°C and muscle tone reaches a level similar to the rigidity of death. The patient's appearance resembles mixedema. Death generally results from ventricular arrhythmias or pulmonary edema (26). Fever is the rise in body temperature in response to an inflammatory stimulant and is rarely above 42°C. There may be mild cognitive changes at this level but coma does not develop. Therefore, the coma seen in febrile patients usually results from the toxic neuronal effect of the primary inflammatory process.

Hyperthermia is body temperature of 42°C and above and causes stupor and coma. It is usually seen as a result of heat stroke. Malignant neuroleptic syndrome, malignant hyperthermia and serotonin syndrome are rare causes of hyperthermia seen following drug / anesthesia administration. These syndromes may be distinguished by history, clinical presentation and various symptoms (5,27,28).

Hypoxia – Ischemia Hypoxia is lack of oxygenation in the brain and may be considered in four distinct categories: (1) hypoxic hypoxia, (2) anemic hypoxia, (3) ischemic hypoxia, and (4) histotoxic hypoxia. Hypoxic hypoxia occurs when there is inadequate oxygen in the blood, and is most commonly seen in pulmonary diseases and hypoventilation. As it affects all organs, it results in cardiac decompensation and ischemia. In anemic hypoxia the amount of oxygen in the blood is adequate but there is a decrease or modification in the hemoglobin that is required for its transport. In ischemic hypoxia the brain flow in the brain decreases independently of the amount of oxygen in the blood. The most common causes are myocardial infarction decreasing cardiac output, cerebrovascular diseases or arrhythmias. Histotoxic hypoxia, on the other hand, occurs when electron transport chain is impaired due to toxic agents, most commonly carbon monoxide and cyanide intoxication (5, 21). Acute anoxia causes symptoms in a few seconds, if oxygen deprivation lasts more than 1-2 minutes, it may result in stupor, coma and permanent damage. The most sensitive structures are the hippocampus and the cerebellar Purkinje cells (5, 29).

Infections Although infectious agents including bacteria, viruses, rickettsia, protozoa and nematoda may all affect the brain parenchyma, only bacteria and viruses (and Rocky Mountains fever caused by rickettsia) result in consciousness disorders (2). CNS infections may mimic several other causes of coma. Fast and accurate diagnosis is especially important in this disease group because treatment may be life saving, furthermore prevent sequelae. As infection symptoms and agents may be atypical and patients in an encephalopathy picture for other reasons, especially in patients with a suppressed immune system, recognizing CNS infections may be difficult (30). Acute bacterial meningitis very frequently impair consciousness. In a large patient series, 69% of the patients were found to have a wakefulness defect and 14% coma and stupor. In the same series, the most common agent of bacterial meningitis was found to be *Streptococcus pneumoniae*

Table 3. Non-infectious diseases that may mimic acute CNS infections

| Acute meningitis | Acute encephalitis |
|-------------------------------|---------------------------------------|
| Behçet's disease | Acute disseminated encephalomyelitis |
| Ruptured cyst | Acute hemorrhagic leucoencephalopathy |
| Drug induced meningitis | Toxic encephalopathy |
| Meningismus | Behçet's disease |
| Sarcoidosis | Serum disease |
| Systemic lupus erythematosus | Systemic lupus erythematosus |
| Vogt Koyanagi Harada syndrome | Vogt Koyanagi Harada syndrome |

(53%) and *Neisseria meningitidis* (37%). In the clinic, the typical triad of acute bacterial meningitis is stiff neck (nuchal rigidity), fever and impaired consciousness; only 1/3 of the patients in this series had all three of these symptoms (31).

Viruses cause brain pathology via various mechanisms: (1) causing primary CNS infections, i.e. acute viral encephalitis, (2) parainfectious encephalomyelites developing during or following measles, mumps or rubella infections, and (3) slowly progressing viral infections mostly seen in immunosuppressed patients. Viral encephalites are usually characterized with a quieter and more heterogeneous picture and are more difficult to recognize (2, 32).

Various non-infectious diseases may mimic CNS infections. Some of the clinical conditions that may be confused with acute CNS infections are shown in Table 3.

It should be remembered that toxic or septic encephalopathy developing as a result of systemic infections may also cause brain dysfunction from confusion to coma (5).

• **Psychogenic coma**

Psychogenic coma, or psychogenic nonresponsiveness may be difficult to distinguish from neurogenic coma. The patient may be completely unresponsive in some psychiatric disorders, including, (1) conversion reactions developing on a background of anxiety, depression or personality disorder, (2) catatonia seen in disorders including schizophrenia, and (3) simulation. The physician encounters two challenges in psychogenic coma; it is impossible to obtain a medical history from the patient and to determine the psychological status, furthermore somatization accompanies many neurologic disorders. In this case the only clinical diagnostic tool is proving whether the patient's complaints are based on an anatomical and physiological rationale. Eyelids, pupils, spontaneous eye movements and caloric test may help distinguish these two conditions. The eyelids of a patient in a coma do not resist to passive opening and slowly close when let go. On the other hand, the patient's eyelid resists examination in psychogenic coma. Whereas the pupils are isochoric and responsive to light in psychogenic coma, pupil reflex is preserved in coma, but mydriasis occurs when the eyelid is opened. Patients with psychiatric wakefulness disorder cannot mimic the spontaneous, roving eye movements occasionally seen in true coma. If the patient does not have a concurrent vestibular disorder the caloric reflex is always normal. The fastest differential diagnostic tool is EEG; a healthy pattern with baseline alpha rhythms and responses to eye opening and sound is seen in pseudocoma (5, 33, 34).

The neuropathophysiology of coma

• **Structural coma**

Two main mechanisms are thought to be involved in structural coma: (1) direct destruction of the tissue, and (2) displacement and damage of the tissue through compression. ARAS must have structural damage for a lesion to directly impair wakefulness. Only bilateral damage can cause coma in subcortical or cortical fields, whereas unilateral midline lesions in the brain stem and diencephalon including tumours, hematomas, infarcts and infections (e.g., abscesses) may be enough to damage the reticular formation. Mass lesions may compress the ARAS structures, causing intracranial pressure and interfering with its function. They may directly compress the reticular formation or displace brain tissue and indirectly apply pressure on the ARAS and compress it (35). Mass lesions including tumours, hematomas, and abscesses may compress brain tissue, causing destructive and

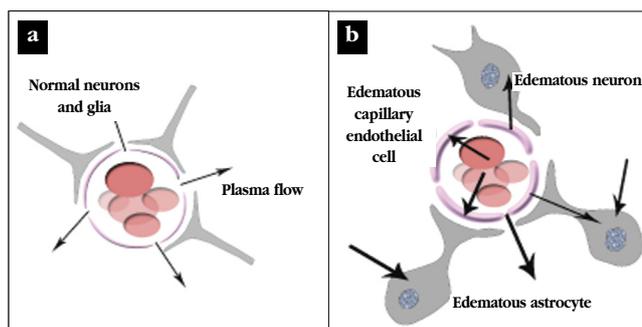


Figure 2. Types and mechanisms of brain edema
a) Vasogenic edema, b) Cytotoxic edema

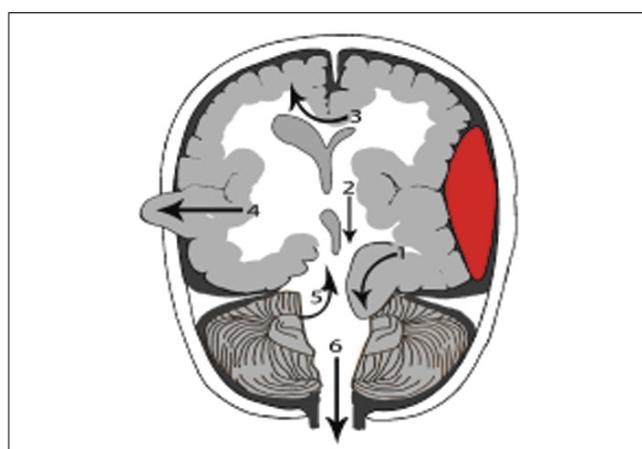


Figure 3. Types of herniation
1. Uncal herniation, 2. Central herniation, 3. Subfalcian herniation, 4. Transcalvarial herniation, 5. Upward herniation of the brain stem, 6. Tonsillar herniation

compressive damage, as well as brain edema, contributing to further increase in intracranial pressure (5).

- Coma related to metabolic causes and diffuse brain damage

The mechanisms of coma related to metabolic causes and diffuse brain damage are not yet clearly identified. It is thought that bilateral diffuse disorder occurs as a result of inflammatory response, metabolic disorder and neurotransmitter interference and wakefulness may be impaired. Processes including trauma, infections or surgical procedures may cause systemic inflammation, as a result of which the dysregulation occurring in inflammatory mediators in the circulation may cause endothelial dysfunction, impairment of the blood-brain barrier, decrease in brain functions and finally death in neuroglial cells. Interleukin (IL-10) and tumour necrosis factor alpha (TNF- α) are two cytokins responsible for neurodegeneration (36). The common feature of metabolic encephalopathy is the lack of substrates required in the brain or the inability to utilize the substrates efficiently. Pathologic processes such as hepatic failure, uremia, vitamin deficiencies, acidosis and alkalosis impair oxidative mechanisms and affect the level of consciousness. It is not always possible to determine the exact endogenous metabolic toxin that causes coma. A correlation has been found between coma and high levels of acetone particles in diabetic coma, small molecular toxins which would probably respond to dialysis in uremia, and levels of ammonia 5-6 fold above normal in hepatic coma. Swelling of neurons and loss of KCl as a result of intracellular sodium loss plays a role in the pathophysiology of hyponatremia (37). Neurotransmitters including acetylcholine, cerebral monoamines (dopamine, serotonin, etc.) GABA, glutamate and histamine are chemicals involved in maintaining wakefulness. Cholinergic neurons are found widely throughout the brain and absence of acetylcholine has been associated with delirium and coma. Factors including glucose deficiency, decrease in oxygen and thiamine deficiency may impair wakefulness by causing decrease in acetylcholin synthesis. GABA is known to have the highest inhibitor activity and its activity is found to increase in hepatic encephalopathy. Various drugs and toxins (benzodiazepins etc.) impair wakefulness by acting via GABA receptors (38, 39). The oxygen requirements of the brain are not met due to various reasons in acute ischemia, and the overall cerebral metabolism collapses. If the brain remains without oxygen for 1-2 minutes, especially if there is an underlying cerebrovascular disease, loss of consciousness and coma may occur and can be permanent. If the lack of oxygen persists for more than 4 minutes neuron death starts (40).

- Brain edema

Two distinct cellular mechanisms of brain edema can be seen in the brain tissue, namely vasogenic edema and cytotoxic edema.

Local tissue ischemia develops in brain tissue as a result of the pressure created by space occupying lesions. The pressure causes the tissue to strain and damage, and compress small arteries, disrupting cellular blood flow. Hematomas, tumours and some inflammatory lesions have the ability to form new blood vessels where they are located (angiogenesis), but the endothelium of the newly formed vessels cannot form the blood-brain barrier. As the endothelial permeability of these vessels is high, plasma flows to the extracellular field, forming vasogenic edema (Figure 2).

Ischemia and inability to provide energy to cells result in the impairment of the ionic gradient. Neurons are depolarized, but as repolarization is not possible sodium influx continues. The cells become hyperosmolar and start swelling, creating cytotoxic edema. As a result, adjacent tissues are progressively under pressure, raising pressure increases local ischemia and therefore an unfortunate vicious cycle is created. As this process continues, calcium starts to accumulate within the cells and this triggers apoptosis resulting with cell death (41, 42). Recent studies have observed that fluid channels called aquaporin 4 (AQP 4) are involved in both types of edema. Glial AQP 4 appears to contribute to the swelling of astrocytes and therefore to cytotoxic edema, and also to extracellular fluid absorption (43).

In the clinic, patients usually start to decompensate rapidly when cytotoxic edema starts to develop (44).

- Increased intracranial pressure (IICP)

Increased intracranial pressure (IICP) can be classified in four based on etiology and pathophysiologic mechanisms: a) Parenchymal IICP related to intracerebral lesions, b) Vascular IICP related to cerebral blood flow disorders, c) IICP related to disorders of CSF dynamics, and d) idiopathic IICP (45).

When increased intracranial pressure is chronic, it does not cause brain dysfunction, unless it is above 600 mmHg; major signs and symptoms are papilledema and headache. In conditions causing acute increased intracranial pressure such as venous thrombosis, trauma induced hemorrhage or encephalitis, cerebral perfusion pressure (the difference between the average arterial pressure and intracranial pressure) is affected; when this value is above 45-50 mmHg, there will be hemodynamic disorders in the brain. The ionic flow in neurons is disrupted because of energy restrictions and tissue edema develops. This process further increases intracranial pressure, thus creating another vicious cycle. The acute increases in intracranial pressure may cause paroxysmal neurologic symptoms in a wide spectrum (43).

- **Brain herniation**

The structures comprising the total volume of the brain are brain tissue, cerebrospinal fluid (CSF) and some blood. The intracranial space is divided into 4 intracranial compartments by the septums located in the dura: right and left supratentorial compartments, infratentorial compartment and spinal subarachnoidal space. A normal brain may compensate the additional volume created by the growing mass by displacing the CSF to a certain extent. As the mass grows the amount of CSF to be displaced decreases and the least increase in volume causes acute increase in intracranial pressure in that compartment. As a result the difference in pressure between adjacent compartments increases and brain tissue moves between compartments. This process is called brain herniation. There are 6 major patterns of brain herniation (Figure 3):

Uncal herniation: Uncal herniation occurs when a lesion located in the hemispheres slips in the medial temporal lobe, by the side of the cerebellar tentorium and the tentorial gap and compresses the mesencephalon. The most notable sign of this condition is pupillary dilation resulting from the compression of the dorsal part of the oculomotor nerve. Eye movements may be somewhat restricted and exophthalmia may be found. Wakefulness is always impaired due to compression of ARAS located in the mesencephalon, involvement of the diencephalon or impairment of the blood flow in the arteries to the brain stem. Hemiparesis accompanies the clinical picture as a result of the cerebral peduncle compressing the uncus. As hemiparesis can be contralateral (compression of the peduncle on the same side) or ipsilateral (compression of the cerebral peduncle on the other side in the Kernohan notch) it does not have any localizing value. However, although the side of the dilated pupil is of great value for the localization of the lesion, even dilated fixed pupils are shown to be misleading for localization (47). Visual defects developing as a result of the compression of the posterior cerebral artery can usually not be examined in coma patients because they are not awake and take place in a wide spectrum of disorders from homonymous hemianopsia to cortical blindness (48).

Central herniation: Occurs as a result of the compression of the diencephalon. If the pressure is high enough, the diencephalon compresses the mesencephalon, and even folds over it. Small penetrating arteries supplying the diencephalon branch directly from the Willis polygon; when these arteries compress, ARAS is exposed to ischemia at the diencephalon level and therefore wakefulness is impaired. In severe cases diabetes insipidus

develops as the pituitary gland is compressed. This anatomic shift is thought to cause a more progressive clinical picture with a worse prognosis than uncal herniation (49).

(Sub)Falxian herniation: When a hemispheric mass compresses the brain tissue at the level of the cerebral falx, the compression caused in the pericallosal and callosomarginal arteries causes ischemia. The brain edema caused by ischemia further increases the mass effect.

Transcalvarial herniation: Occurs when brain tissue in cerebral hemispheres squeezes out of a skull fracture, and is also called external herniation. This may occasionally occur iatrogenically following a craniotomy.

Upward herniation of the brain stem: The brain stem herniates upwards as a result of an acutely developing posterior fossa lesion. Dorsal mesencephalon and adjacent arteries, and cerebral aqueductus are mainly affected. The patient can develop restriction of upward gaze, and even Parinaud syndrome and acute hydrocephalus.

Tonsillar herniation: Cerebellar tonsils are pushed against the foramen magnum and compress the bulb; as a result, the circulation in the fourth ventricle is obstructed and there is an acute increase in intracranial pressure. Furthermore, the patient may have acute hypotension due to the involvement of the bulb and there may be sudden respiratory arrest (2, 5, 50).

Conclusion

The evaluation of the coma patient should be performed by physicians in various disciplines. A detailed investigation and deductive effort will be needed to discover the underlying cause of coma. In recent years widened use of sophisticated investigation methods such as MRI has changed priorities in investigations and provided great ease in discovering the etiology of coma. However, imaging methods should not be the only help relied upon when searching for etiology because numerous causes of coma are solely metabolic or toxic and imaging methods cannot provide any clues. Various factors may cause coma, and a multitude of pathophysiological mechanisms are involved in the development of coma. The physician should consider the patient as a whole, integrate the information provided through history, physical examination and diagnostic tools with his/her theoretical knowledge. As mechanisms causing coma are better understood, treatments targeting specific causes have been developed, and are currently being used in intensive care units.

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