# METABOLIC ENCEPHALOPATHIES

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SUMMARY – Metabolic encephalopathies may be important complications of many diseases in patients treated at intensive care units. The term metabolic encephalopathies encompasses a large variety of different conditions of the brain. Neurologic signs of metabolic encephalopathies, ancillary tests, differential diagnosis, etiology, pathophysiology and treatment are discussed in this review. Metabolic encephalopathies are usually multifactorial in origin and play an important role not only as diseases *per se* but also for monitoring the severity of decompensating organ functions during deteriorating primary diseases.

Key words: *Brain diseases – metabolic, diagnosis; Brain diseases – metabolic, physiopathology; Critical care; Shock – septic, diagnosis; Shock – septic, physiopathology; Multiple organ failure, diagnosis*

## Introduction

Metabolic or secondary encephalopathies are disorders in which a disturbance of cerebral function (encephalopathy) results from failure of some other organ system (e.g., heart and circulation, lungs and respiration, kidneys, liver, pancreas and the endocrine glands); in fact in many cases they are multifactorial in origin. Encephalopathies can be defined as diffuse, multifocal and functional cerebral disturbances, which are not caused by inflammation, in other words, it is not encephalitis, and, at least in the beginning, is not combined with morphologic changes. Primary encephalopathies are caused by different, mostly genetically defined disturbances of amino acid, carbohydrate and lipid metabolism.

Metabolic encephalopathies are most common complications of many diseases in patients treated at intensive care units and their clinical manifestation can be taken as a warning of deterioration or beginning of organ dysfunction. Reversibility of metabolic encephalopathy relates to successful treatment of systemic dysfunction, subject of progress in the field of internal medicine.

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## Etiology

Metabolic encephalopathies are caused by hypoxic-ischemic states, a variety of organ dysfunctions, systemic diseases and toxic agents (Table 1). Alcohol is the single most frequent exogenous toxic agent[1].

## Pathophysiology

Up to now, the pathophysiologic mechanism of metabolic encephalopathies has not been completely understood. The basic precondition is probably a disturbance of blood brain barrier with changes in the amino acid and neurotransmitter profile. Evidence from clinical and experimental research shows that vascular factors, infection and endotoxins have a distinctive role in the pathophysiology[2]. Histopathologic studies found tissue hypoxia, edema and necrosis in vascular and special types of hepatic encephalopathies. Morphologic changes of astrocytes including hyperplasia of protoplasmic astrocytes that resembles Alzheimer type II cells are found at the cellular level[3,4].

## Clinical Featres

Metabolic disturbances are frequent causes of impaired consciousness. Their presence must always be considered when there are no focal signs of cerebral disease and both the imaging studies and the cerebrospinal fluid are normal.

*Table 1. Major causes of metabolic encephalopathies*

***Hypoxia***
- Anemia
- Pulmonary disease
- Alveolar hypoventilation

***Ischemia***
- Cardiovascular disease (including cardiac arrest)
- Stokes-Adams syndrome, cardiac arrhythmias
- Hypersensitive carotid sinus
- Microvascular diseases
- Hyperviscosity syndrome
- Hypotension
- Hypertension

**Systemic diseases**
- Hepatic disease
- Renal disease
- Pancreatic disease (gastrointestinal)
- Malnutrition (vitamin deficiency)
- Endocrine dysfunction (hypoglycemia or hyperglycemia and hyperosmolar state)
- Acid-base, electrolyte and fluid imbalances
- Vasculitis
- Infections and sepsis
- Malignancy (paraneoplastic syndromes)

**Toxic agents**
- Alcohol, sedatives (barbiturates, narcotics, tranquilizers)
- Psychiatric medications (tricyclic antidepressants, anticholinergic drugs, phenothiazine, monoamine oxidase inhibitors)
- Heavy metals
- Organic phosphates, solvents
- Other drugs (corticosteroids, penicillin, anticonvulsants)

The main feature of the reversible metabolic encephalopathies is mental confusion with disorientation and inattentiveness, accompanied in some instances by asterixis, tremor and myoclonus. This state may progress to stupor and coma[1,5]. Slowing of the background rhythms in the electroencephalogram parallels the severity of the metabolic disturbance[6,7].

In Table 2, the acquired metabolic diseases of the nervous system are classified according to their most common clinical presentation.

Clinical signs in metabolic encephalopathies may be divided into global cerebral signs and focal cerebral signs. Global signs predominate and may be accompanied by mostly less pronounced focal signs, depending on the severity of encephalopathy. In early stages, global signs include confusion and slight cognitive disturbances as well as psychomotor hyperactivity (agitation, hallucination, delusions, delirium) and autonomic dysfunctions (Cheyne-Stokes respiration, cardiac arrhythmias or arrest, vertigo, nausea, vomiting, vasomotor and sudomotor disturbances). In more severe cases, seizures, global brainstem signs with oral and facial automatisms, pathologic reflexes, tremor, asterixis, multifocal myoclonus and abnormalities of muscle tone (paratonia, decorticate and decerebrate posturing) are found. The expression of these signs is variable even in the clinical course of the same patient.

Focal cerebral signs may originate from the hemispheres (visual disturbances, aphasia, apraxia, hemispas-

*Table 2. Classification of the acquired metabolic disorders of the nervous system*

1. Metabolic diseases presenting as a syndrome of confusion, stupor or coma
   - Hypoxic-hypotensive encephalopathy
   - Hypercapnia
   - Hyperglycemia
   - Hypoglycemia
   - Hepatic failure
   - Reye's syndrome
   - Uremia
   - Disturbances of sodium, potassium, and changes in osmolality

2. Metabolic diseases presenting as a progressive extrapyramidal syndrome
   - Acquired hepatocerebral degeneration
   - Hyperbilirubinemia, kernicterus
   - Hypoparathyroidism

3. Metabolic diseases presenting as cerebellar ataxia
   - Hypothyroidism
   - Hyperthermia
   - Celiac disease

4. Metabolic diseases causing psychosis or dementia
   - Cushing disease and steroid encephalopathy
   - Thyroid psychosis and hypothyroidism
   - Hyperparathyroidism
   - Pancreatic encephalopathy

tic, hemiatactic, hemisensory syndromes, reflex and muscle tone changes) or/and from the brainstem (cranial nerve disturbances, e.g., oculovestibular, pupillomotor; nystagmus, gaze deviations, brainstem reflex disturbances, dysarthria, dysphagia, respiratory disturbances, atactic, paretic, sensory syndromes – hemi-, quadri-, alternating; reflex changes, myoclonus)[8].

The clinical course of encephalopathies is variable. Coma may develop acutely or a fluctuating level of consciousness may be present. This fluctuating individual course is a characteristic feature in the clinical assessment of different types of encephalopathies.

The history and clinical examination of consciousness, respiration, pupillary reactions and ocular movements, spontaneous movements, muscle tone and posture must be carefully taken along with the battery of additional medical and laboratory examinations.

Laboratory examinations provide reliable clues to most of the causes of metabolic encephalopathies, and the following determinations should be done: serum Na, K, Ca, glucose, BUN, $NH_3$, acid-base status and osmolality. It is important to remember that the brain may be damaged, even irreversibly, by a disturbance of blood chemistry that is no longer present when the patient is first seen.

On differential diagnosis it is necessary to consider vascular diseases of the brain including intracranial hemorrhages, sinus venous thromboses, infectious or immunologic diseases of the brain, brain tumors and other causes of raised intracranial pressure, then malignant hyperthermia, malignant neuroleptic syndrome, acute adrenal failure and thyroid storm[1,5].

## Hypoxic/Anoxic and Ischemic Encephalopathy

The basic disorder is the lack of oxygen supply to the brain, which results from failure of the heart and circulation or of the lungs and respiration. The medical conditions that most often lead to hypoxic/ischemic encephalopathy are (1) myocardial infarction, ventricular arrhythmia, external or internal hemorrhage, and septic or traumatic shock (in all of which cardiac function fails before that of respiration); (2) suffocation (from drowning, strangulation, aspiration, compression of the trachea or tracheal obstruction); (3) carbon monoxide poisoning; (4) diseases that paralyze the respiratory muscles (Guillain-Barré syndrome, myasthenia) or damage the central nervous system diffusely but the medulla specifically; and (5) general anesthesia, during which the patient is exposed to inspired gas that is oxygen-deficient.

Clinical features depend on the degree of hypoxia as well as on the speed of the advancement of hypoxia. Mild degrees of hypoxia induce inattentiveness, poor judgement and motor incoordination. Profound anoxia may be well tolerated if arrived gradually; that could be seen in some patients with advanced pulmonary disease who are fully awake even if their arterial oxygen pressure is in the range of 4 to 5 kPa. This level, if occurring abruptly, causes coma[9].

The most severe degrees of the lack of oxygen are usually caused by cardiac irregularities, especially by cardiac arrest. Consciousness is lost within seconds, but recovery will be complete if breathing, oxygenation of blood and cardiac action are restored within 3 to 5 min. In case of hypothermia or barbiturate coma recovery is complete if the restoration of cardiopulmonary functions is completed within 8 to 10 min. The outcome of cardiac arrest is generally poor in the majority of cases. Even when the rescusciation is successful, patients have to overcome the subsequent complication of anoxic/ischemic encephalopathy during the next days or the next week. The reported results of recent studies suggest that therapeutic hypotermia has a beneficial effect on the neurologic outcome in survivors[10,11].

The main consequence of cardiac arrest is coma. If there is a state of complete unawareness and unresponsiveness with abolition of all brainstem reflexes, and natural respiration cannot be sustained, with no electrical activity on electroencephalogram (EEG), but only cardiac action and blood pressure are maintained, the state is referred to as brain death syndrome. Upon resuscitation patients with stabilized breathing and cardiac activity may be profoundly comatose with the motionless and divergent eyes but reactive pupils, the limbs inert and flaccid or rigid, and the tendon reflexes diminished. Generalized convulsions and isolated or grouped myoclonic twitches may supervene. If the damage is severe, coma persists, decerebrate postures may be present or may occur in response to painful stimuli, and there are bilateral Babinski signs and hyperthermia. Death may terminate this state or the individual may survive for an indefinite period in persistent vegetative state[12].

Data derived from many large series show that six months after cardiac arrest the estimated survival rate is in the range between 11% and 22%. Sixty percent of patients were found to have moderate to severe cognitive deficits three months after cardiac arrest. One year later about one half of the survivors still had moderate to severe neuropsychologic sequels that were thought to be permanent. These figures change with hypothermia applied after successful cardiac resuscitation in the field[10,11].

The main prognostic variables for poor outcome are the absence of pupillary light reflexes and the absence of motor responses to pain on day 3, bilateral absence of early cortical SSEP within the first week, existence of biochemical markers (serum neuron-specific enolase and S-100 protein), myoclonic status, and on EEG burst suppression pattern or the development of alpha-coma in deeply comatose patients[13,14]. The permanent neurologic sequels or posthypoxic syndrome observed most frequently include persistent coma or stupor, with a lesser degree of cerebral injury, dementia with or without extrapyramidal signs, visual agnosia, extrapyramidal syndrome with cognitive impairment, choreoathetosis, cerebellar ataxia, intention or action myoclonus, Korsakoff amnesic state and seizures[1].

A relatively uncommon phenomenon is delayed postanoxic encephalopathy, where an initial improvement over 1 to 4 weeks is followed by a relapse characterized by apathy, confusion, irritability or agitation and mania. Most patients survive this second episode, but some are left with serious mental and motor disturbances. In others there is progression with weakness, shuffling gait, diffuse rigidity and spasticity, incontinence, coma and death after 1 to 2 weeks. Postmortem examination showed widespread cerebral demyelination[5].

Treatment of hypoxic-ischemic encephalopathy is directed mainly to the prevention of a critical degree of hypoxic injury. Once cardiac and pulmonary functions have been restored, there is experimental evidence that reducing cerebral metabolism by hypothermia and barbiturates may prevent the delayed worsening, however, controlled trials outside cardiac arrest have failed to show neurologic benefit, furthermore, hypotension resulting from barbiturates is itself detrimental. Oxygen may be of value during the first hours but is probably of little use after the blood has been well oxygenated. Corticosteroids may theoretically help reduce brain swelling, but their use has not been corroborated by clinical trials. Seizures should be controlled by antiepileptic drugs but after a few hours seizures are replaced by myoclonus and clonazepam may be useful in their control[2,15].

## Hepatic Encephalopathy

Hepatic encephalopathy is a consequence of liver function disturbance and/or portal-systemic shunts. It is graded from I (slight) to IV (coma, unresponsive)[16], as shown in Table 3.

The pathophysiology of this extensively investigated encephalopathy refers to neurotoxins (ammonia metabolism, short and medium chain fatty acids, mercaptans, phenols) and altered neurotransmission including false neurotransmitters and benzodiazepine-like substances[3]. Recent observations indicate that the increased GABAergic neurotransmission is due to the increased concentrations of substances like benzodiazepines. They are produced from bacterial metabolism in the gut, bypass the liver and bind benzodiazepine receptors in the brain[17]. While the practicality of using benzodiazepine receptor antagonists (e.g., flumazenil: single doses of 0.2-0.3 mg given every 1-3 min for a total dose of 2 mg, or infusion of 2 mg in 15 min, or in continuing infusion 2 mg/h) in the treatment of hepatic encephalopathy remains to be determined, there is evidence that the administration of these drugs does result in transient awakening in many patients[18]. Important predisposing factors for developing encephalopathy include an excess of protein derived from the diet or gastrointestinal hemorrhage; hypoxia, hypokalemia, metabolic alkalosis, electrolyte depletion, excessive diuresis, use of sedative or hypnotic drugs, and constipation.

EEG is a sensitive and reliable indicator of impending coma. The usual abnormality consists of paroxysms of bilaterally synchronous slow or triphasic waves in the delta range, which predominate frontally[6,7].

In most patients, the syndrome does not evolve beyond the stage of mild mental drowsiness and confusion, with

*Table 3. Stages of hepatic encephalopathy*

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|---|---|
| I | Slight confusion, decreased psychomotor activity (occasional hyperactivity), inverted sleep pattern, hypo/hypersomnia, short attention span, low perception, impaired calculation, mood changes, anxiety/apathy, coordination and handwriting disturbances, tremor. |
| II | Drowsiness, slow response, poor memory, disorientation for time, inappropriate behavior, asterixis, ataxia, dysarthria. |
| III | Stupor, confusion, delirium, paranoia, disorientation, amnesia, perseveration, hyperventilation, nystagmus, hyperreflexia, Babinski sign, rigidity, muscle twitching, incontinence, possibly epileptic seizures. |
| IV | Coma, abnormal flexion or extension responses, brisk oculocephalic responses, dilated pupils and sluggish responses to light. In the early stages of coma reaction to painful stimuli, later unresponsive. |

asterixis and EEG changes. Hepatic coma evolves over a period of days to weeks and often terminates fatally or the symptoms may regress completely or partially and then fluctuate in severity for several weeks or months. There is a group of patients (many of them experience repeated attacks of hepatic coma) in whom irreversible mild dementia and a disorder of posture and movement gradually appear; the condition is referred to as chronic hepatocerebral degeneration[1,5].

Hepatic encephalopathy due to fulminant hepatic failure is in most cases caused by viral hepatitis and acetaminophen poisoning. The main complications of fulminant hepatic failure is cerebral edema, which is one of the major causes of mortality (80% to 90% of patients die). Other severe complications are epileptic seizures (caused by hypoglycemia), bleeding from the upper gastrointestinal tract, combination with renal dysfunction (hepatorenal syndrome), and concomitant respiratory alkalosis and hypotension[19,20].

Treatment of hepatic encephalopathy means treatment of liver disease. Few effective means of treating this disorder include restriction of dietary protein, reducing bowel flora by oral administration of neomycin or kanamycin, and the use of enemas (lactulose). The sustained use of oral neomycin carries a risk of renal damage and ototoxicity. Ultimately, in cases of intractable liver failure, transplantation becomes a treatment of last resort. Other methods of treatment, the value of which still remains to be established, include the use of dopamine agonist (e.g., bromocriptine) and of keto-analogues of essential amino acids. The keto-analogues should provide a nitrogen-free source of essential amino acids and bromocriptin should enhance dopaminergic transmission. The administration of branched-chain amino acids may result in considerable improvement in mental status, but their effects have been variable and associated with an increased mortality[1,5,21].

## Renal Encephalopathies

Diseases of the kidney such as glomerulonephritis, pyelonephritis, interstitial nephropathies and arteriosclerotic diseases lead to uremia with the accumulation of toxic substances causing encephalopathy. Clinical signs are quite clear, especially in acute renal failure which is mostly seen in shock, by nephrotoxic agents, thrombotic thrombocytic purpura, myoglobinuria and immunosuppressive treatment.

Uremic encephalopathy presents like other encephalopathies with changing expression of global cerebral symptoms such as fluctuating disturbance of consciousness and agitation, but also with additional signs such as hyperpnea, hyperreflexia, multifocal myoclonus, tremor, asterixis, brain stem signs with different types of nystagmus, and muscle tone abnormalities. A variety of involuntary motor phenomena, such as twitches, convulsions, fasciculations, arrhythmic tremor, myoclonus, chorea and asterixis, form a condition known as the uremic twitch-convulsive syndrome. Confusion, disturbances of sensory perception, hallucinations and delusions sometimes assume the form of toxic psychosis with paradoxical reactions to sedative drugs[22].

As in other acute encephalopathies, EEG shows stages of generalized slowing with an excess of delta and theta waves within 48 hours of the onset of renal failure. The grade of slowing increases with increased serum creatinine[6].

The pathophysiology of uremic encephalopathy remains uncertain. Animal experiments have shown biochemical changes in the brain, such as elevated level of parathyroid hormone and concomitant calcium content. Cerebral edema is notably absent. In fact computed tomography (CT) scans and magnetic resonance imaging (MRI) often show cerebral shrinkage with chronic renal failure, likely due to hyperosmolality. Altered excretion of drugs may lead to their accumulation and contribute to the development of uremic encephalopathy. A state of twitching and convulsions in rats can be produced by the injection of urea alone. Uremia is frequently associated with hypertension and a major problem arises in distinguishing the cerebral effects of uremia *per se* from those of severe hypertension, a condition known as pseudouremia or hypertensive encephalopathy[22].

Complications of dialysis refer to dialysis disequilibrium syndrome, dialysis encephalopathy and Wernicke's encehalopathy. Dialysis disequilibrium syndrome is characterized by headache, nausea, vomiting, blurred vision, muscle twitching, hypertension, tremor, asterixis, multifocal myoclonus, disorientation, and in severe cases psychosis, stupor and coma. The symptoms tend to occur in the third or fourth hour of dialysis and last for several hours. Nowadays, it is believed that the symptoms should be attributed to water intoxication due to inappropriate secretion of antidiuretic hormone[22]. Progressive dialysis encephalopathy (dialysis dementia) is a subacute severe, frequently fatal neurologic disease characterized by speech disturbances, involuntary motor phenomena, seizures and features of Alzheimer's disease. The current view of its pathogenesis is that it represents a form of aluminum intoxication. The aluminum may be derived from the dialy-

sate or from orally administered aluminum gels. In recent years, the disorder has practically disappeared[23,24]. Wernicke-Korsakoff syndrome caused by thiamine depletion has a classic triad of symptoms: mental symptoms (e.g., global confusional state, disorientation in time and place, Korsakoff amnesic state), ataxia and ocular abnormalities (e.g., ophthalmoplegia with nystagmus and diplopia)[25].

Treatment of uremic encephalopathy consists of dialysis or renal transplantation. Improvement of symptoms may not be evident for a day or two after institution of dialysis. Convulsions often respond to relatively low doses of anticonvulsants, but if there are associated metabolic disturbances such as hyponatremia, the seizures may be difficult to control[22].

## Encephalopathy with Hypoglycemia/ Hyperglycemia

When the level of blood glucose has declined to about 2.5 mmol/L, the initial symptoms occur, i.e. anxiety, hunger, sweating, headache, palpitation, vomiting, confusion, drowsiness, and occasionally overactivity and bizarre behavior. In the next stage, motor restlessness, muscular spasms and decerebrate rigidity, convulsions and myoclonus or focal neurologic deficits (e.g., hemiplegia) occur. Blood glucose levels of approximately 1.0 mmol/L are associated with deep coma, dilatation of pupils, pale skin, shallow respiration, slow pulse and hypotonia of limb musculature. In this stage, injury to the brain may be irreparable and recovery may be incomplete. The most common causes of hypoglycemic encephalopathy are accidental or deliberate overdose of insulin or an oral diabetic agent, insulin-secreting tumor of the pancreas, depletion of liver glycogen in prolonged alcoholic binge, starvation or acute liver disease, and chronic renal insufficiency. Treatment of all forms of hypoglycemia consists of immediate correction of the hypoglycemia[26,27].

Clinical features of diabetic acidosis consist of dehydration, fatigue, headache, abdominal pain, stupor, coma, Kussmaul type of breathing and often positive Babinski sign. Usually the condition has developed over a period of days in young diabetics with current infection and/or inadequate insulin therapy. Treatment consists of prompt administration of insulin and repletion of intravascular volume. In hyperosmolar nonketotic hyperglycemia the blood glucose is extremely high, over 40 mmol/L but ketoacidosis does not develop or is mild. There is also hemoconcentration and prerenal azotemia. Most of the patients are elderly diabetics, but some were not previously known to have diabetes, with current infection, enteritis, pancreatitis or taking a drug known to upset diabetic control such as thiazides, prednisone or phenytoin. Clinical features include seizures, focal neurologic deficits such as hemiparesis or homonymous visual field defect. The mortality is high. Fluids should be replaced cautiously, using isotonic saline and potassium, and correction of the markedly elevated blood glucose requires relatively small amount of insulin, since these patients often do not have insulin resistance[1,5].

## Septic Encephalopathy

This encephalopathy has gained most interest in recent years due to advances in the management of severely ill patients at intensive unit. Detection of its signs indicates that the progressive basic disease has spread to the nervous system. Multiorgan failure with and without sepsis is the leading cause of mortality in critical care accounting for 10% to 50% of deaths[28]. In sepsis, plasma and brain amino acids are deranged with a decrease in branched chain amino acids and an increase in most neutral amino acids in the brain, similar to the findings in portasystemic encephalopathy. Aromatic amino acid levels correlated with APACHE II scores and mortality. Scores and mortality rate are higher in shock patients with higher levels of ammonia and sulfur-containing amino acids[29]. This encephalopathy has become an important factor in surgery dealing with sepsis. The principal clinical features are alterations in the level of consciousness and EEG changes. Since encephalogram is a sensitive index of brain function in septic encephalopathy, it would be useful to monitor suspected patients with EEG as a predictor of the severity of encephalopathy and associated mortality[6,7].

## Conclusion

Metabolic encephalopathies represent a crucial problem in severely ill patients. They may develop in the clinical course of deteriorating systemic disease as well as complications during treatment at critical care unit. Signs of metabolic encephalopathy may be an early indication of developing complications.

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Sažetak

## METABOLIČKE ENCEFALOPATIJE

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Metaboličke encefalopatije su značajne komplikacije koje se javljaju u mnogih bolesnika liječenih u jedinicima intenzivnog liječenja. Termin "metaboličke encefalopatije" odnosi se na širok spektar poremećaja funkcije mozga za vrijeme teške, kritične bolesti. U ovom članku prikazani su neurološki simptomi, mogućnosti dijagnostičkih metoda, kao i etiologija, patofiziologija te terapija metaboličkih encefalopatija. Metaboličke encefalopatije su u svojoj osnovi multifaktorijalne, a prepoznavanje njihovih simptoma ima važnu ulogu u ranom otkrivanju zatajivanja organskih sustava za vrijeme pogoršavanja osnovne bolesti.

Ključne riječi: *Bolesti mozga – metaboličke, dijagnostika; Bolesti mozga – metaboličke, fiziopatologija; Kritična skrb; Šok – septički, dijagnostika; Šok – septički, fiziopatologija; Višeorgansko zatajenje, dijagnostika*