Clinical practice review

Neurologic Complications of Critical Illness: Part I. Altered States of Consciousness and Metabolic Encephalopathies

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ABSTRACT

Objective: *To review the metabolic encephalopathies and neuromuscular abnormalities commonly found in the critically ill patient in a two-part presentation.*

Data sources: *A review of articles reported from 1980 to 2002 and identified through a MEDLINE search on metabolic encephalopathy, polyneuropathy and myopathy in critical illness.*

Summary of review: *An alteration in the conscious state can be caused by space occupying lesions or infections of the central nervous system. However, in the critically ill patient a metabolic encephalopathy is often the cause of an acute confusional state or a reduced state of consciousness. There is no specific treatment for the metabolic encephalopathies as they commonly resolve when the underlying disorders (e.g. sepsis, renal failure, hepatic failure, electrolyte disturbance) are corrected. Management may also require judicious pharmacological and/or physical restraint in the case of the acute confusional states and ensuring an adequate airway, ventilation and circulation in the case of a reduced state of consciousness, while the underlying disorder is corrected and the encephalopathy resolves.*

Conclusions: *In the critically ill patient a metabolic encephalopathy is commonly the cause of confusion, disorientation, agitation, drowsiness or coma. Sedative agents and tranquilisers may be required as well as management of the airway, ventilation and circulation while the underlying disorder is corrected to allow the encephalopathy to resolve.* (**Critical Care and Resuscitation 2002; 4: 119-132**)

Key words: Metabolic encephalopathy, critically ill, confusion, coma, delirium, hepatic encephalopathy, septic encephalopathy

Most of the sensory pathways of the body relay impulses generated from sense organs via 3 or 4 neurons to particular areas of the cerebral cortex. To maintain the cerebral cortex in a state of wakeful consciousness, sensory impulses relay via collateral connections to a loosely grouped collection of neurons located in the upper brainstem and medial thalamus known as the reticular activating system (RAS).

Consciousness cannot exist without a normally functioning RAS and widespread participation of the cerebral cortex. While alterations in consciousness occur in the critically ill patient with cerebral disruption caused by trauma and space occupying lesions, thalamocerebral function can also be altered due to disorders of the internal body environment caused by metabolic abnormalities (e.g. hypoglycemia, hyponatraemia, anoxia, azotemia or hepatic failure), sepsis, drugs or toxins. These disorders can present as an altered conscious state and are often grouped together as the metabolic encephalopathies.

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ALTERED STATES OF CONSCIOUSNESS

Acute confusional states

Confusion is a state of cognitive impairment where the patient has a reduction in coherence, comprehension and capacity to reason. Disorientation is a state of cognitive impairment characterised by impaired attention, concentration, and an inability to register immediate happenings and to recall them later. The confused patient is usually subdued, not inclined to speak and is physically inactive.

Delirium is a state of confusion that is accompanied by increased arousal which is characterised by agitation, delusions, hallucinations, autonomic overactivity (e.g. insomnia, diaphoresis, fever, tachycardia, tremor, diarrhoea) and even seizures. An hallucination is a false sensory perception, occurring without any external stimulus. A delusion is a fixed irrational belief not consistent with the patient's cultural norms.[1]

Confusion and delirium always signify a disorder of the nervous system. They may be the major manifestations of head injury, seizure, drug toxicity or withdrawal, metabolic disorder (e.g. hepatic, renal, pulmonary or cardiac failure) systemic infection, meningitis or encephalitis, or a chronic dementing disease. Confusion in the postoperative period is common but at times so subtle as to escape attention.

Causes

An acute confusional state, particularly in the elderly, may develop in association with any of the conditions listed in Table 1.

Treatment

Treatment of an acute confusional state includes resuscitation and supportive therapy, correction of the underlying disorder (Table 1), tranquilisers, sedatives and occasionally physical restraint to protect the patient from excessive motor or autonomic activity.

Resuscitation and supportive therapy

While treatment of the underlying disorder takes effect, fluid, glucose and electrolyte maintenance and B group vitamin supplementation are standard considerations in the management of the confused and disorientated patient. There should also be a reduction in the number of procedures that cause sleep deprivation, provision of a familiar environment (e.g. pictures of family, clock, flowers, cards and radio or television) and allowing familiar individuals (e.g. family) to visit frequently (but not for prolonged periods).[2,3] Any discussion with the patient should appear helpful and agreeable, and not appear as a disagreement or hindrance (even when dealing with the patient's delusions) as the latter tends to only increase the agitation.

Table 1. Causes of an acute confusional state

Sepsis
pneumonia, urinary tract infection, wound infection, septicaemia
Postoperative
Hypoxia, hypercapnia, pain, full bladder, anaesthetic drugs, drug withdrawal
Post cardiopulmonary resuscitation
Trauma
burns, pancreatitis, fat embolism, heat stroke, hyperpyrexia
Cerebrovascular disorders
Transient ischaemic attack, stroke, subdural haematoma, hydrocephalus
Acute drug withdrawal (e.g. 1-3 days after ceasing)
sedative, tranquilliser, opiate, antidepressant, ethyl alcohol, corticosteroids
Drug toxicity
antidepressants, tranquillisers, sedatives, anticholinergics, antihistamines
sympathomimetics, amphetamines, phencyclidine, lysergic acid diethylamide, aminophylline
local anaesthetic agents, opiates, corticosteroids, quinolones, digoxin, cimetidine, aluminium hydroxide, sucralfate
Metabolic disorders
Hepatic, renal, cardiac or respiratory failure
thyrotoxicosis, myxoedema, Cushing's disease, Addison's disease, porphyria,
hypocalcaemia, hypercalcaemia, hyponatraemia, hypernatraemia, hypokalaemia, hypophosphataemia
hypomagnesaemia, alkalosis, alkalosis, hypoxia, hypercapnia, hypoglycaemia, D-lactic acidosis
Environmental factors (e.g. 'intensive care syndrome')
sleep deprivation, noise, foreign and windowless environment
sensory 'excess', diurnal cycle impairment, communication impairment, dependency, immobilisation

Pharmacological therapy

a. *Benzodiazepines:* these act by combining with the benzodiazepine receptor α subunit, which in turn enhances the effect of GABA on the chloride channel, so that chloride ions enter the cell to increase the resting membrane potential and inhibit excitation.[4,5] Both GABA and benzodiazepines

attach to the GABA and benzodiazepine receptor, respectively, at the cell surface. By themselves, benzodiazepines do not open the Cl^- channel or cause neuronal inhibition.

While intravenous diazepam (5 mg hourly up to 20 mg) may provide prolonged sedation in some patients (as it is metabolised to the active compounds of 3-hydroxydiazepam, oxazepam and desmethyldiazepam), in the severely agitated patient its action is often be short lived and only partially effective. The water soluble agent, midazolam, is hydroxylated by a hepatic cytochrome P_{450} to α-hydroxymidazolam which is conjugated to α-hydroxymidazolam glucuronide and eliminated by the kidney.[6] In one study in which midazolam was used to produce basal sedation, using 0.3 mg/kg over 30 min (20 mg/70 kg) followed by an infusion at 0.06 mg/kg/hr (4 mg/70 kg), accumulation of the drug effect was not noted and normalisation of mental state occurred 1.5 hr after discontinuing the infusion.[7]

However, in intensive care patients or patients with hepatic disease, the half-lives of the parent drug of all benzodiazepines generally increase by up to two to three times (i.e. the half-life of diazepam may increase up to 10 days and the half-life of midazolam may increase up to 10 hr in the critically ill patient).[8,9]

b. *Phenothiazines:* these are D_1 and D_2 dopamine receptor blockers, which may block M_1 muscarinic, α_1-adrenergic, α_2-adrenergic and H_1 histamine receptors as well. Their antipsychotic activity is due largely to their D_2 dopamine receptor blocking effect in the limbic system.

Chlorpromazine is the standard phenothiazine tranquiliser. An initial oral or intramuscular dose of 50 - 100 mg is commonly administered to manage an agitated patient and its effect is usually assessed 1 hr later. If required, further doses of 50 - 100 mg may be administered hourly. While up to 1000 mg has been used in some severely disoriented patients, if 200 - 600 mg does not produce the desired effect, then supplemental doses of a benzodiazepine (e.g. midazolam 2 - 10 mg) will act synergistically and produce profound sedation which often lasts for 6 - 8 hr. While an intravenous bolus dose of 2.5 - 10 mg of chlorpromazine can cause severe hypotension, an intravenous infusion at 10 - 20 mg/hr can be used safely. The elimination half-life of chlorpromazine is 24 - 48 hr.

The side-effects of phenothiazines include dry mouth, constipation, urinary retention and blurred vision (due to a muscarinic receptor blocking effect), hypotension and hypothermia (due to an α_1-adrenoreceptor blocking effect). Parkinsonian side-effects occur due to nigrostrial dopamine receptor blockade which may cause acute extrapyramidal effects (e.g. oculogyric crisis or akathisia, which are treated with intravenous benztropine 1 - 2 mg) or a late-onset, tardive dyskinesia.[10] The other side effects include QT_c interval prolongation with torsade de pointes, malignant neuroleptic syndrome, leucopaenia, eosinophilia, cholestatic jaundice and photosensitivity.

c. *Butyrophenones:* haloperidol (5 - 10 mg i.v.) is the most commonly used butyrophenone in the intensive care unit, although it may not provide the same sedative effect as chlorpromazine and may not be as effective as chlorpromazine for the severely agitated patient. In one study haloperidol infusions ranging from 3 to 25 mg/hr were used successfully to control agitation in critically ill patients,[11] although they also described complete heart block, ventricular tachycardia and QT_c prolongation (with the risk of torsade de pointes) as side effects, indicating that this form of therapy may not be without risk.[12]

d. *Atypical neuroleptic agents*

i) *Clozapine*. Clozapine has 5HT receptor (largely $5HT_{2A}$) as well as D_2 dopamine receptor antagonism, reducing the disturbing extrapyramidal side effects that are often associated with the phenothiazine and butyrophenone tranquilisers. It is effective in 50% of patients unresponsive to conventional neuroleptics. The dose ranges from 300 to 900 mg a day. Side effects include sedation and anticholinergic properties (due to H_1 histamine and M_1 muscarinic receptor antagonism, respectively), agranulocytosis (weekly blood tests for 18 weeks then monthly blood tests should be performed in all patients during therapy), seizures, hypotension, hypersalivation, weight gain, myocarditis and rarely cardiomyopathy.[13]

ii) *Risperidone*. Risperidone has $5HT_2$ as well as D_2 receptor antagonism and while it is not as effective as clozapine, it does not cause agranulocytosis and has a lower rate of extrapyramidal adverse effects. The dose ranges from 2 to 6 mg a day (e.g. 1 - 3 mg 12-hourly).

iii) *Olanzapine*. Olanzapine has $5HT_2$ as well as D_2 receptor antagonism but unlike clozapine and risperidone, does not antagonise α_2-adrenergic receptors as well, and has not been associated with a reduction in seizure threshold. The dose

ranges from 5 to 20 mg a day and is usually given as a single daily dose. Side effects include sedation, somnolence, weight gain and anticholinergic properties (due to H_1 histamine and M_1 muscarinic receptor antagonism, respectively). While it does not cause agranulocytosis and has a lower rate of extrapyramidal adverse effects, neutropenia, seizures and neuroleptic malignant syndrome have been reported.

iv) *Sertindole, ziprasidone and quetiapine*. These are newer atypical neuroleptic agents which are also reported to have lower rates of extrapyramidal adverse effects. However QT_c prolongation (sertindole) and sedation (ziprasidone) indicate that they are not free of adverse effects.

e. *Ethyl alcohol and nicotine*. In the acutely ill alcohol or cigarette dependent patient, intravenous 5% ethanol in 5% dextrose (i.e. 50 mL of 100% alcohol per litre of 5% dextrose) infused at 50 - 100 mL/hr, or nicotine patches, respectively, have been used successfully for agitation and delirium tremens prophylaxis. For alcohol dependence, the serum ethanol levels are reportedly low or unmeasurable and patients are usually able to be weaned from the mixture after 3 - 7 days.[14,15]

f. *Beta-adrenergic blockers*. The sympathetic effects of acute agitation following withdrawal of sedative drugs (e.g. tachycardia, hypertension, diaphoresis) have been treated successfully with beta-adrenergic blockers (e.g. propranolol 40 - 80 mg orally 4 hourly, or 5 mg intravenously 2- to 4-hourly).

Physical restraint

To protect the patient from self-injury or to stop the patient removing intravenous lines, drainage tubes or respirator connections, physical (e.g. glove and feet restrainers to limit limb movement) may occasionally be required. They should be placed at the wrists (or secure each finger with strapping) and ankles to restrict upper and lower limb movement without allowing the patient to inflict any self-harm.

Reduced states of consciousness

Consciousness is a normal state of arousal and cognitive function. Clouding of consciousness is a state in which both arousal and cognition is impaired. Stupor is a sleep-like state from which the patient can only be aroused by vigorous and persistent stimulation. Coma is a sleep-like state from which the subject cannot be aroused.[1,16] Clouding of consciousness and stupor are usually attended by some degree of confusion.

Causes

There are many conditions that can cause a reduced state of consciousness and may lead to coma (Table 2). In the intensive care patient, a common clinical problem is that of a patient who remains unconscious when the acute illness has resolved and the sedative, opiate and relaxant drugs have been withdrawn.[17]

The commonest reason for the continued state of drowsiness or coma is the presence of one or a combination of the disorders that can cause a metabolic encephalopathy. In the absence of structural brain damage, these are usually reversable when the underlying cause (e.g. sepsis, renal failure, hepatic failure) is corrected.[18-20] The diagnosis of the cause of a reduced state of consciousness or coma is made from the:

Clinical examination (e.g., patients who have coma due to a metabolic encephalopathy, c.f. coma due to a structural brain disorder, usually have a pupillary response to light, flexor or no response to pain, are hypotonic, and do not have a positive Babinski reflex).

Plasma biochemistry: for glucose, urea, creatinine, osmolality, sodium, potassium, calcium, phosphate, magnesium, transaminases, complete blood picture, platelet count, coagulation studies, drug levels and culture.

Arterial blood gases: for pH, HCO_3^-, PCO_2 and PO_2 estimations.

Radiological studies: skull, cervical spine X-ray, cerebral computed tomography (CT) or magnetic resonance (MR) imaging.

Lumbar puncture: performed in the presence of meningeal irritation and in the absence of a space-occupying lesion on CT scan. In septic encephalopathy the cerebrospinal fluid (CSF) and the CT scan are usually within normal limits.[19]

EEG: while this has been reported to be a sensitive index of brain function in septic encephalopathy,[21] (see later) in practice EEG recordings at the intensive care unit bedside are rarely performed as they are often subject to artifact and are not helpful.

Treatment

The management of a patient in coma requires management of the underlying disorder as well as:

Resuscitation

This is performed to ensure an adequate airway, ventilation and circulation, and an adequate delivery of oxygen and glucose to the brain. Seizures are managed by treating the underlying condition (e.g. hypoglycaemia, hyponatraemia, etc.) and with antiepileptic therapy.

Table 2 Causes of coma

Metabolic encephalopathy
- Global hypoxia (e.g. cardiac arrest, carbon monoxide poisoning, near drowning)
- Drug intoxications, poisonings, or overdosage (e.g. drug accumulation)
- Sepsis, septicaemia, multiple trauma,
- Reye's syndrome, dialysis induced
- Hypo- and hyper-
  - tension, thermia, capnia, glycaemia, natraemia,
  - calcaemia, magnesaemia
- Hypophosphataemia, hypokalaemia
- Hepatic failure, renal failure
- Cofactor deficiency thiamine, pyridoxine, vitamin B_{12}
- Pancreatitis, porphyria
- Small vessel disease
  - fat embolism, air embolism,
  - post-cardiopulmonary bypass,
  - cholesterol embolism,
  - systemic lupus erythematosus,
  - disseminated intravascular coagulation,
  - thrombotic thrombocytopenic purpura,
  - bacterial endocarditis
- Myxoedema, thyrotoxicosis, hypopituitarism

Psychogenic 'coma'
- Hysteria, catatonic schizophrenia

Cerebral functional abnormality
- Concussion, postepileptic, vasovagal attack, syncope, electrocution

Intracranial lesions
- Subdural, epidural, intracerebral, space-occupying lesions
- Cerebral or brainstem haemorrhage, embolus, infarct
- Subarachnoid haemorrhage, closed head injury
- Encephalitis, meningitis

General care of an unconscious patient

a) *Physiotherapy*. Passive leg movement 8-hourly, splinting of ankles and wrists to prevent contractures.
b) *Eye care*. As the corneal reflex is often depressed, the eyes are taped at the angles to ensure that they are closed at all times to reduce the incidence of corneal trauma, keratopathy and infection.[22] Artificial tears and antibiotic ointment are used if the conjunctiva is exposed, and if the cornea is exposed other methods may also be necessary to ensure closure of the lids,[23] including the use of a Donaldson eye patch (using a Velcro fastener), a 5 O' silk suture of upper and lower lid margins, polyacrylamide gel patches with high water content or cling wrap. While conjunctival oedema may be caused by trauma to the unprotected eye, it may also be caused by severe extracellular oedema.[24] Severe nosocomial eye infections in the critically ill patient are usually caused by *Pseudomonas aeruginosa* which often arises from *P. aeruginosa* chest infections.[25] Damage to the eye with keratopathy and corneal trauma requires urgent opthalmological advice.
c) *Posture*. Neutral limb and head postures are carefully maintained to reduce tendon, muscular and nerve injury (e.g. brachial plexus injury associated with hyperextention of the upper limb).
d) *Mouth and nose toilet*. This is performed to reduce the collection of secretions with subsequent development of sinusitis (particularly when nasal and oral tubes are present). Oral nystatin (100,00 U/mL, 5 mL 8-hourly) is used to prevent candida infection.
e) *Pressure point care*. Regularly shifting the patient's position is required to prevent dermal ulceration (e.g. bed sores of sacrum, heels elbows, occiput), peripheral nerve injury and rhabdomyolysis.
f) *Aseptic management of cannulae and tubes*. These include central venous and Swan-Ganz catheters, suctioning of endotracheal tubes, urinary catheters, enterostomy bags, and abdominal drains.
g) *Fluid, electrolyte and nutritional care*.
h) *Pulmonary embolism prophylaxis*.

The vegetative state

This is a state of consciousness that may follow an episode of severe brain injury, where the individual appears to awaken after 2 - 4 weeks but has no conscious intelligence. Unlike brain death, these individuals have a functioning brain stem, although they appear to have no higher cortical function.[1] The characteristic features of the vegetative state include:[26]

a) no evidence of awareness of self or the environment and an inability to interact with others,
b) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli,
c) no evidence of language comprehension or expression,
d) intermittent wakefulness (manifest by the preservation of sleep-wake cycles),
e) sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care,
f) bowel and bladder incontinence, and
g) variably preserved cranial nerve reflexes (e.g. pupillary, oculocephalic, corneal, oculovestibular, gag) and spinal reflexes.

If the vegetative state persists for longer than one month it is classified as a *persistent* vegetative state. Recovery of consciousness from a posttraumatic persistent vegetative state is unlikely after 12 months and therefore is regarded as a *permanent* vegetative state (PVS) if it lasts 12 months or more.[27] However, improvements in consciousness after posttraumatic persistent vegetative states lasting 15 months[28] and 21 months[29] have been reported, prompting some to believe that improvement in consciousness after 12 months (particularly in young patients) may not be rare.[28] Recovery from a nontraumatic persistent vegetative state after three months is rare and therefore regarded as a PVS if it lasts 3 months or more.

Other abnormalities of consciousness

Certain other clinical states are prone to be misinterpreted as stupor or coma. Akinetic mutism refers to a partially or fully awake patient who is able to think but remains immobile and mute, particularly when unstimulated. The condition may result from damage in the regions of the medial thalamic nuclei, the frontal lobes (particularly situated deeply or on the orbitofrontal surfaces), or from hydrocephalus. Catatonia is an hypomobile and mute syndrome associated with a major psychosis. The patient often appears awake with eyes open but will make no voluntary or responsive movement. Usually, eyelid elevation is actively resisted, blinking occurs in response to a visual threat and the eyes move concomitantly with head rotation. It is characteristic but not invariable for the limbs to retain the posture in which they have been placed by the examiner, no matter how unusual. The appearance is superficially similar to akinetic mutism, but clinical evidence of brain damage is lacking.

The locked-in state describes a pseudocoma in which the patient has no means of producing speech or volitional limb, face, and pharyngeal movements in order to indicate that he or she is awake. Usually vertical eye movements and lid elevation remain unimpaired, thus allowing the patient to signal. Infarct-ion or hemorrhage of the ventral pons, which transects all descending corticospinal and corticobulbar pathways, is the usual cause. A similar state occurs as a result of total paralysis of the musculature in severe cases of Guillain-Barré syndrome and pharmacologic neuromuscular blockade.

METABOLIC ENCEPHALOPATHIES

A variety of disorders may cause an alteration in consciousness by interrupting the delivery of energy substrates (e.g. hypoxia, ischemia, hypoglycemia) or by altering neuronal excitability (e.g. hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, hepatic and renal failure). These are often grouped as a metabolic encephalopathy (c.f. coma due to a structural brain disorder) and usually have a pupillary response to light, flexor or no response to pain, are hypotonic and usually do not have a positive Babinski reflex (although a Babinski reflex may be positive in patients with a previous cerebrovascular accident or hepatic encephalopathy).

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to confusional states characterised by disordered perception, frequent hallucinations, delusions and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain and anxiety. The term ICU psychosis has often been used to describe this when it is found in the intensive care unit patient. Ultimately, the psychosis resolves with improvement in the underlying illness and a return to familiar surroundings.

In the ICU setting, there are also several metabolic causes of an altered level of consciousness. These include:

Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric syndrome caused by advanced liver disease and is graded from I to IV (Table 1).

Table 1 Clinical grading of hepatic encephalopathy

Grade	Clinical state	Survival
I	Mild mental confusion, euphoria, depression Slowness of mentation and affect Slurred speech, disorder of sleep	100%
II	Accentuation of Grade 1, drowsy, confused disoriented, inappropriate behaviour Sphincter control lost	70%
III	Stuporous but arousable, speech incoherent	40%
IV	Comatose, not responsive to pain or decerebrate rigidity, dysconjugate or skew position of eyes. Seizures	20%

Chronic hepatic insufficiency with portal-systemic shunting is often associated with episodes of altered states of consciousness known portal-systemic encephalopathy (PSE). It is characterised by drowsiness, confusion, disordered sleep, slurred speech, inappropriate behaviour followed by agitation, confusion, delirium and coma. The sign of asterixis (i.e. flapping tremor or an irregular flexion-extension movement of the outstretched hand and flexed wrist) is usually found in

patients who have Grade II or III encephalpathy. However, asterixis is a nonspecific finding as it may also occur in patients who have other metabolic or toxic encephalopathies (e.g. hypercapnia, uraemia, hypokalaemia, hypophosphataemia, hyponatraemia, hypomagnesaemia, hypoglycaemia, hyperglycaemia), severe sepsis, severe cardiac failure, polycythaemia, drug toxicities (e.g. pethidine, salycilates, phenytoin, barbiturates, valproate and carbamazepine) and even during standard treatment with psychopharmacologic agents (e.g. carbamezapine, clozapine, lithium, levodopa).[30-32] A worsening of the encephalopathy may be precipitated by gastrointestinal bleeding, hypokalaemic alkalosis, sepsis, sedatives, constipation or excess dietary protein.

Patients who survive numerous episodes of PSE may be left with chronic neurological abnormalities of tremor, asterixis, dysarthria and ataxia known as chronic progressive hepatocerebral degeneration. Other conditions that may be confused with PSE include other metabolic encephalopathies (e.g. hypoglycaemia, hyponatraemia), cerebral disorders (e.g. subdural haematoma, meningitis), Wernicke's encephalopathy (an acute thiamine deficiency characterised by a triad of acute confusion and disorientation, ataxia of gait with nystagmus, and opthalmoplegia - mainly a bilateral 6th nerve palsy)[33] and Korsakoff's psychosis (characterised by an antegrade and retrograde amnesia, dementia, psychosis and diffuse cerebral atrophy).

The toxins and mechanisms which may be responsible for the development of hepatic encephalopathy include:[34]

Ammonia

Approximately 40% of the daily ammonia production is generated from bowel organisms acting on gastrointestinal protein and urea, and 50 - 60% is produced from systemic deamination and deamidation of amino acids.[35] The daily urinary excretion of nitrogenous compounds is approximately 460 mmol (400 mmol as urea, 40 mmol as ammonium, 12 mmol as creatinine, 2 mmol as amino acids, and 5 mmol as uric acid). Ammonium excretion may increase up to 300 mmol/day during severe acidosis.

In the central nervous system, ammonia combines with alpha-ketoglutarate to form glutamate, which in turn combines with ammonia (a reaction that requires energy from ATP) to form glutamine. This reaction depletes cerebral tissue of the citric-acid cycle intermediate, alpha-ketoglutarate, increases glutamate and consumes ATP.[36] The increase in CSF glutamate found in patients with portal-systemic shunting correlates well with the degree of encephalopathy.[37]

While high ammonia levels are toxic and hyperammonaemia without hepatic failure has been associated with coma,[38] the clinical picture of acute ammonia toxicity differs from that of hepatic encephalopathy.[38,39] Moreover, ammonia levels correlate poorly with depth of coma, and methods that have reduced ammonia levels have not been associated with improvement in level of consciousness. Nevertheless, fatty acids and mercaptans exacerbate the encephalopathic effects of ammonia,[40] and alkalosis and hypokalaemia increase the intracellular concentration of ammonia, which may explain some of the disparate observations in relation to the serum ammonia level and state of consciousness.[41,42]

Amino acid imbalance with abnormal neurotransmitters

In hepatic failure the plasma amino acid profile becomes abnormal. Ammonia liberates glucagon which stimulates gluconeogenesis,[43] which stimulates skeletal muscle catabolism and increases plasma amino acid levels. The uptake of branched chain amino acids (BCAA) by skeletal muscle is increased due to hyperinsulinism, which decreases the plasma BCAA levels and allows the elevated levels of plasma aromatic amino acids (i.e. phenylalanine, tyrosine and tryptophan) to remain. As both the BCAA and the aromatic amino acids share a common blood brain barrier carrier system, the reduction in plasma BCAA levels allows the blood brain barrier carrier to transport increased quantities of aromatic amino acids into the CSF.[43,44] The high levels of tyrosine and phenylalanine decrease the synthesis of the neurotransmitters, dopamine and noradrenaline, and the increased levels of tryptophan increases the cerebral levels of the inhibitory neurotransmitter, serotonin.[39] False neurotransmitters such as octopamine and phenylethanolamine (derived from bacterial action on tyramine in the gut) are increased, increasing cerebral levels of these agents.

However, contrary to the theories of amino acid imbalance or abnormal neurotransmitters, decreased levels of octopamine and increased levels of noradrenaline and dopamine have been observed in patients dying from hepatic encephalopathy.[45]

Mercaptans

Methionine is metabolised to a group of compounds known as mercaptans, which experimentally are able to cause coma.[26]

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter and GABA or GABA-like substances that arise from the bowel flora are normally cleared by the liver. In hepatic failure, high levels of circulating GABA are often recorded, and in the presence of other toxins which increase the blood brain barrier permeab-

ility, GABA may enter the cerebral tissue causing an encephalopathy.[46,47] An endogenous benzodiazepine (i.e, GABA receptor facilitator) has also been postulated as a cause for hepatic encephalopathy,[48-50] and benzodiazepine-like immunoreactivity has been found in the CSF of patients with hepatic encephalopathy.[51]

Glutaminergic dysregulation

Glutamate mediated neurotransmission is altered in acute liver failure with experimental evidence of a decreased neural reuptake of glutamate, increased extracellular glutamate and an imbalance of glutamine receptor neurotransmission, resulting in an increase in N-methyl-D-aspartate (NMDA) receptor-mediated transmission. While NMDA receptor antagonists improve the encephalopathy associated with hepatic failure, they do not afford any significant protection against the development of cerebral oedema or intracranial hypertension resulting from acute hepatic failure. To explain these findings, it has been suggested that the changes in cerebral glutamate regulation may be a consequence (rather than a cause) of cerebral oedema due to hepatic failure,[52] although in the experimental animal, ammonia-induced astrocyte swelling can be prevented by inhibiting glutamine synthetase (and therefore glutamate production).[53]

Manganese

Similarities between manganese toxicity and chronic hepatic encephalopathy along with the observation that concentrations of manganese in whole blood and in the basal ganglia in patients with end stage liver disease is often increased, has led to the hypothesis that chronic hepatic encephalopathy might be due to manganese toxicity.[54] Manganese toxicity (e.g. parkinsonism and cholestatic liver disease) may occur in patients who are receiving manganese supplementation with long-term parenteral nutrition.[55] However, therapy with chelating agents to reduce manganese levels has not yet been reported in patients with chronic hepatic encephalopathy.

Treatment

Resuscitation and management of precipitating factors

By treating the precipitating factors (i.e. sedatives, hypokalaemia, metabolic alkalosis, sepsis), reduction in dietary protein to 50 g/day, glucose and oral or intravenous supplements of vitamin K, vitamin C, thiamine, folate and other B group vitamins.

Lactulose

Lactulose is a synthetic nonabsorbable disaccharide that passes unchanged to the lower bowel (unless there is bacterial overgrowth in the small bowel when resistance to lactulose may occur), where it is metabolised by anaerobic bacteria to produce lactate, acetate, formate and carbon dioxide. It has a cathartic effect, thereby reducing the time available for the production and absorption of gastrointestinal toxins as well as promoting faecal excretion of nitrogen. It also acidifies the bowel contents, thereby trapping ammonia (by converting ammonia to its ionised form, which is less easily absorbed from the intestine) and suppresses proteolytic bacterial flora.[56] The ammonia level may also be reduced, by bacteria incorporating it into bacterial proteins.[57] The standard dose of lactulose (i.e. 30 mL 8-hourly) is adjusted to produce two to three bowel actions a day, and may be combined with neomycin to produce an additive effect.[57] In one report, lactulose enemas (300 mL of 50% lactulose added to 700 mL of tap water, as a retention enema for 1 hr) improved the clinical grade of hepatic encephalopathy within 12 hr.[58]

Lactilol

Lactilol is a nonabsorbable disaccharide powder that is an alternative to lactulose.[59] While it has not been widely used, some believe that it is the treatment of choice for hepatic encephalopathy.[60]

Neomycin

Oral neomycin 1 g 6-hourly (or any nonabsorbable aminoglycoside e.g. oral gentamicin 200 mg 6-hourly) for 1 - 2 weeks (i.e. only during the acute decompensation) is often used in patients who have chronic hepatic encephalopathy, whereas it is seldom used in patients who have acute hepatic failure (particularly when associated with renal failure unless serum levels are monitored), because up to 5% can be absorbed and lead to nephrotoxic and ototoxic effects.

Nonabsorbable aminoglycosides (e.g. neomycin, gentamicin) primarily inhibit the growth of bacteria that are poor fermenters of nonabsorbable disaccharides (e.g. enterobacteria, staphylococcus, enterococcus), rather than anaerobic bacteria that are efficient ferm-enters of nonabsorbable disaccharides (e.g. *Lactobacillus*, *Bacteroides*, and *Clostridia* spp.). While some studies have shown an additive effect of nonabsorbable disaccharides (e.g. lactulose, lactilol) with a nonabsorbable aminoglycoside, the beneficial effects are not consistent. Nonetheless, it is recommmended that a combination of a nonabsorbable disaccharide with a nonabsorbable aminoglycoside should be tried in any patient with chronic hepatic encephalopathy who does not have an optimal response to either agent alone.[61] Oral metronidazole (200 mg 6-hourly) is as effective as neomycin and may be used in patients who have renal

failure or neural deafness, although it should not be used in combination with lactulose, as it inhibits the growth of anaerobic bacteria. Vancomycin (1000 mg 12-hourly) may also be effective, even in patients who have lactulose resistant portal systemic encephalopa-thy.[62] Eradication of *Helicobacter pylori* may also be of benefit in patients with chronic hepatic failure and encephalopathy.[63]

Flumazenil

Flumazenil is a benzodiazepine receptor antagonist and has been shown to produce clinical and EEG improvement in up to 40% of patients with hepatic encephalopathy.[64-66] However, its effect is short-lived, and it has no effect in patients who have cerebral oedema.[49]

Dietary protein

In patients who have no excessive protein losses and who are not bleeding, the enteral or parenteral daily protein intake may be reduced to 50 g. Prophylactic proton pump inhibitors (omeprazole 40 mg daily) or H_2 antagonists (ranitidine 150 mg daily) will reduce the incidence of upper gastrointestinal bleeding.[67]

Other therapy

Branched chain amino acids (BCAA) are thought to have no effect in patients who have chronic hepatic encephalopathy,[68,69] although in one randomised double-blind trial, patients with chronic encephalopathy became neurologically normal when treated with oral BCAA.[70]

As zinc is a metalo-coenzyme necessary for the metabolism of ammonia to urea, zinc deficiency (which is common in cirrhotic patients due to increased loss of zinc in the urine) should be corrected (using 600 mg zinc sulphate oral zinc sulphate daily for 1 - 3 months).[63]

Acute hepatic encephalopathy

Grade IV hepatic encephalopathy is usually associated with episodes of elevated intracranial pressure (ICP) and cerebral oedema and while chronic hepatic failure with PSE can lead to Grade VI coma, it usually does so in over a period of days to weeks. However, patients with fulminant hepatic failure (FHF) may develop Grade IV coma with severe cerebral oedema over hours, due to mechanisms not fully understood. As the major cause of death in FHF is cerebral oedema, treatment is often directed at reducing intracerebral pressure. This includes;

Osmotherapy

Ideally, all patients who have grade IV encephalopathy should have an intracranial pressure monitor and therapy directed at keeping the cerebral perfusion pressure greater than 50 mmHg. This usually means that all episodes of increased cerebrospinal fluid pressure greater than 25 mmHg, for 15 min or longer, or greater than 30 mmHg for 1 min or longer, are treated.[1,71] The oedema is predominantly cytotoxic[72] and may be responsive to mannitol (e.g. 0.25 g/kg 2-hourly)[1,73] hypertonic saline (10 - 20 mL of 20% i.e. 34 - 68 mmol, 2 hourly up to a serum sodium of 155 mmol/L) or ultrafiltration (if the patient is in renal failure).[73]

Thiopentone and hypothermia

If the raised ICP is resistant to osmotherapy (or ultrafiltration), thiopentone (10 mg/kg in 30 min followed by 5 mg/kg/hr for 3 hr then 1 mg/kg/hr),[74] or moderate hypothermia (32 - 33°C)[75] have been used. However, no large studies have been performed showing any benefit of one treatment compared with another. Resolution of intracranial hypertension often precedes all other signs of improvement in patients who recover spontaneously.[76]

N-acetylcysteine. This will prevent paracetamol-induced hepatotoxicity in most cases, if given within 8 hr of ingestion. It is less effective after this time and fails to avert severe hepatotoxicity if given 15 hr or longer after the overdose. Nevertheless, while N-acetylcysteine may not prevent hepatic necrosis if administered later than 15 hr, it reduces the mortality in this group of patients, by reducing encephalopathy and renal failure associated with paracetamol-induced FHF.[77] N-acetylcysteine also inhibits CCl_4 hepatotoxicity by facilitating the detoxification of the active intermediates of CCl_4 produced by P_{450} mixed function oxidase system.[78]

Hepatic support devices. Charcoal haemoperfusion and polyacrylonitrile membrane haemodialysis to dialyse out the middle molecules, have not significantly altered the mortality associated with fulminant hepatic failure in comparison with that associated with standard conservative therapy, and they are now no longer recommended.[1,79]

At present the general belief is that the multiple and complex functions of the liver can only be replaced by using a biologic substrate (i.e hepatocytes), whether in a whole liver (e.g. extracorporeal pig liver perfusion) or in combination with artificial material.[80] Recently, hepatic cell based extracorporeal assist devices have been used with some success in patients with fulminant hepatic failure.[80,81] Nonetheless, while most of the current hepatic support devices are probably safe, no system so far has been shown to be superior or to unequivocally confer significant clinical benefit.[82]

Other therapies. Heparin,[83] corticosteroids,[84,85] exchange transfusion,[86] insulin and glucagon,[87] cross circulation, BCAA,[88] prostaglandin E_1,[89] prostaglandin

E_2,[90] bromocriptine and plasmapheresis have not altered the mortality associated with FHF.[91] Modified intravenous amino acid preparations to normalise serum amino acid levels have also been used but are of no proven value.[39,92] While oral L-dopa has been reported to temporarily improve the conscious level in patients with hepatic encephalopathy,[93] L-dopa, and carbidopa were shown to be no better than a placebo in a controlled trial of patients who had hepatic encephalopathy.[94]

Orthotopic liver transplantation (OTL). With medical therapy, survival in patients with grade IV encephalopathy is 20%. Orthotopic liver transplantation (which normally has a 1-year survival rate of 80%), has a 1-year survival rate of up to 55% in patients with FHF, and may be the only alternative that offers an improved survival in patients who have grade IV encephalopathy.[86,95-98] Auxiliary liver transplantation (i.e. the transplanted liver supplies normal hepatic function while the native liver remains in situ to regenerate and allow discontinuation of immunosuppressive therapy) has been associated with an 68% complete regeneration of the native liver (mainly in patients with FHF caused by hepatitis A, hepatitis B or paracetamol overdose).[99] Usually all patients with FHF who have grade III - IV encephalopathy are considered for OTL,[100] although patients with severe and uncontrolled intracranial hypertension may not benefit from liver transplantation.[101]

Hepatic xenotransplantation has not been successful due to immunologic (e.g. hyperacute rejection, delayed xenograft rejection and a subsequent cellular rejection), physiologic (e.g. different circulating protein, electrolyte and hormonal concentrations) and microbiological (i.e. different pathogen susceptibilities) barriers.[102,103]

Uraemic encephalopathy

In patients with chronic renal failure, a uraemic encephalopathy (with drowsiness, irritability, confusion, seizures) can occur when the plasma urea nitrogen levels reach 50 mmol/L or greater. The encephalopathy may also be due to hyper or hypocalcaemia, desequilibrium syndrome (rapid reduction in extracellular urea levels causing cerebral oedema), hypermagnesaemia or high aluminium levels (i.e. plasma aluminium levels greater than 2 μmol/L, caused by prolonged use of aluminium hydroxide or sucralfate, as 4 g of sucralfate provides 728 - 828 mg of aluminium which is comparable to that during treatment with aluminium hydroxide).[104-106]

Septic encephalopathy

Septic encephalopathy is a diffuse yet reversible cerebral dysfunction that occurs in up to 70% of patients with sepsis.[18,107] The aetiology is most likely multifactorial with the proposed causes including, reduced cerebral blood flow,[108] impaired cerebral oxygen utilisation, cerebral oedema, abnormal neurotransmitter composition (due to alterations in serum amino acid levels similar in some respects to that observed with hepatic encephalopathy)[109-112] and disruption of the blood brain barrier (caused by the circulating inflammatory mediators, tumor necrosis factor-α, interleukin-1, interleukin -2 and interleukin-6).[19,20,113]

It presents clinically with confusion, disorientation, agitation and fluctuations in level of consciousness. In severe cases the decrease in level of consciousness may even result in coma. Bilateral signs of hyperreflexia and grasp reflex may be elicited and abnormal movements such as myoclonus, tremor or asterixis can occur.

The diagnosis of septic encephalopathy is difficult as is first requires the exclusion of structural abnormalities (e.g normal CT and MRI scans), and an absence of other metabolic, toxic, and cerebral infectious (e.g., meningitis or encephalitis) causes. The EEG has been reported to be a sensitive index of brain function with the severity of an encephalopathy being reflected by changes in the EEG from normal, to excessive theta, predominant delta, triphasic waves, and suppression or burst suppression activity.[21] However, as it is difficult to achieve an EEG recording without artifact at the bedside, this investigation is not often performed.

Although patients with septic encephalopathy severe enough to produce coma have a mortality that approaches 50%,[113] this largely reflects the severity of the underlying illness and is not a direct result of the encephalopathy.

There is no specific treatment for septic encephalopathy although successful treatment of the underlying cause of the sepsis almost always results in complete resolution of the encephalopathy, without residual neurological deficits.[20,109]

Other encephalopathies in the critically ill patient

Apart from the numerous electrolyte, endocrine, vascular, toxic and other causes listed in Table 2, hypertensive, postanoxic and D-lactic acidosis are often forgotten as causes of encephalopathy.

Hypertension. Severe hypertension may cause an encephalopathy presenting with severe headache, vomiting, visual disturbances (even transient blindness), transient paralysis, convulsions, stupor and coma, and will usually only occur in previously normotensive individuals if the MAP is 130 mmHg or greater or 180 mmHg or greater in previously hypertensive patients.[114] Pre-eclampsia is a syndrome consisting of hypertension, proteinuria, subcutaneous oedema hyperreflexia and hyperuricaemia. Grand mal convulsions distinguish eclampsia from pre-eclampsia. Eclampsia is not comp-

licated by papilloedema or retinal haemorrhages; thus it is not a form of malignant hypertension but a form of hypertensive encephalopathy.

Postanoxic encephalopathy. This usually only occurs in patients in whom the initial hypoxic insult has been severe enough to produce coma and who awaken after 24 - 48 hr. It can follow severe asphyxia associated with carbon monoxide poisoning, cardiac arrest or strangulation. A similar syndrome may follow hypoglycaemia. It usually presents after a 1 - 4 week lucid interval following the hypoxic event, with gradual neurological deterioration. The clinical features include cognitive, psychiatric, cerebellar, pyramidal and cerebral dysfunction which may progress to coma.[1,115] It is due to a diffuse demyelination of the cerebral hemispheres.

D-lactic acidosis. In patients with a blind-loop or short bowel syndrome, D-lactic acid may be produced by gut microorganisms. This can cause an encephalopathy (e.g. ataxia, dysarthria, confusion, memory loss, fatigue, weakness, behavioural changes, headache, visual changes, nystagmus) when the plasma D-lactate levels are greater than 3 mmol/L.[116]

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