

2 Encephalopathy

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Encephalopathy and Delirium

- ◆ Encephalopathy is an acute confusional state that is accompanied by an alteration in the level of consciousness (drowsiness, stupor, or coma)
 - The term often used interchangeably with delirium
- ◆ Delirium is an acute, fluctuating state of confusion resulting from diffuse or multifocal cerebral dysfunction
 - Delirium is characterized by impaired attention, concentration, orientation, and memory, fluctuations of consciousness, disordered thinking, hallucinations, incoherent speech, and agitation
 - “Loud” delirium: hallucinations and psychomotor agitation
 - “Quiet” delirium: decreased mental acuity and inattention. This is less easily recognized than “loud” delirium but probably equally dangerous. Most common form in the elderly
- ◆ Avoid the notion of “intensive care unit (ICU) psychosis”; implies that encephalopathy is a consequence of the ICU stay and promotes complacency that may slow the search for all reversible precipitants
 - Encephalopathy in the ICU patient is a reflection of underlying illness or fatigue, *NOT* a result of being in the ICU
- ◆ “Sundowning” is often used to describe a delirium that develops in an elderly (usually demented) patient at night with disturbed sleep–wake cycle; again, promotes complacency, so avoid
- ◆ Impact of encephalopathy: increased length of ICU stay, increased mortality, prolonged mechanical ventilation, and increased risk of self-injury (e.g., self-extubation, pulling supporting catheters)

Risk Factors

- ◆ Patients in an ICU are at high risk for encephalopathy because of:
 - Multisystem illnesses and comorbidities
 - Use of psychoactive medications
 - Advanced age
 - Malnutrition

Evaluation

- ◆ ABCs: assess adequacy of airway, breathing, and circulation
 - Vital signs: look for tachycardia, hypotension, and hypoxemia
 - Arterial blood gas (ABG): look for failure of oxygenation or ventilation
- ◆ History
- ◆ Physical examination
- ◆ Labs
 - Glucose
 - Toxicology screen
 - Urinalysis
 - Rule out infection
 - Urine porphobilinogens in selected cases when porphyria is suspected
 - Complete blood count (CBC)
 - Electrolytes (including Ca^{++} , Mg^{++})
 - Liver function tests, serum ammonia
 - Blood cultures
 - Thyroid function tests
- ◆ Diagnostic studies
 - Chest x-ray
 - Head computed tomography (CT)
 - Lumbar puncture (LP)
 - Electroencephalogram (EEG)
- ◆ Avoid sedation

Delirium Scales

- ◆ Need a monitoring and assessment device
- ◆ Many require a verbally responsive patient
- ◆ Intensive Care Delirium Screening checklist developed recently
 - Based on the presence of eight items
 - Altered level of consciousness
 - Inattention
 - Disorientation

- Hallucination or delusions
- Psychomotor agitation or retardation
- Inappropriate mood or speech
- Sleep–wake cycle disturbance
- Symptom fluctuation
- A score of four items on this scale has 99% sensitivity and 64% specificity when used to screen for delirium
- ◆ Confusion Assessment Method (CAM)-ICU
 - Has four features, the evaluation of which can be adapted if the patient is mechanically ventilated. Delirium is present if the patient has both features 1 and 2, and either feature 3 or 4
 1. An acute onset of mental status changes or fluctuating course
 2. Inattention
 3. Disorganized thinking
 4. An altered level of consciousness

Differentiating Features of Encephalopathy, Delirium, and Dementia

- ◆ Dementia is a progressive disease involving disturbances in multiple spheres of cognition and not usually associated with a decreased level of consciousness early on
- ◆ Demented patients are more susceptible to developing encephalopathy

Treatment

- ◆ Focus on determining and treating underlying cause
 - Rapidly reversible causes: treatment
 - Wernicke's encephalopathy: thiamine, glucose
 - Opiate induced: Naloxone
 - Benzodiazepine induced: Flumazenil
 - Modification of environmental factors
 - Allow uninterrupted sleep as often as possible
 - Room with a window or a well-lit room
 - Close observation with frequent redirection and reorientation
- ◆ Symptomatic Treatment
 - May be considered when available and not contraindicated
 - Define goals of treatment (i.e., reduce risk of self-injury, reduce tachycardia, patient comfort)
 - Haldol: PO/IV/IM in small doses, titrated for effect
 - Risk of extrapyramidal side effects and paradoxical agitation
 - Can take up to 10 min to work

- Can worsen delirium in alcohol withdrawal and cocaine-induced encephalopathy. Benzodiazepines are the treatment of choice in these cases
- Sedatives should be avoided if possible
- Midazolam can be used if the patient is at risk of injuring self but repeated doses should be avoided
- If restraints are used for patient safety they should be adjusted and checked periodically to prevent excessive constriction.

Causes and Management of Specific Causes of Encephalopathy

- ♦ Mild systemic illness commonly produces encephalopathy in elderly or demented patients, especially when combined with new medications, fever, or sleep deprivation
- ♦ In the neurocritical care unit causes of altered mentation may be neurologic. Toxic and metabolic causes, however, should not be overlooked and often play a significant role in the neurocritical care setting
- ♦ Toxic
 - Medications commonly used in the ICU
 - Opiates as analgesics
 - MSO₄, fentanyl, meperidine as epidural—rare cause of systemic toxicity
 - Benzodiazepines
 - Propofol
 - Steroids
 - Only in 5% of patients. Those who develop delirium often have an underlying affective or psychotic disorder
 - Acetylsalicylic acid
 - Neuroleptic malignant syndrome (*see* Chapter 4)
 - Encephalopathy, rigidity, hyperthermia, tachycardia, and hypertension are caused by neuroleptic medications such as haloperidol
 - Potentially fatal but can be treated with bromocriptine in mild cases, dantrolene in more severe cases
 - Industrial
 - Organophosphates
 - Symptoms: bradycardia, hypotension, miosis, increased lacrimation, nausea and/or vomiting, diarrhea, encephalopathy, seizures, and coma
 - Treatment: atropine, benzodiazepines, and phenytoin for seizures

- Carbon monoxide
 - Symptoms: Encephalopathy, dizziness, headache, tachycardia, ataxia, syncope and seizures
 - Treatment: 100% oxygen or hyperbaric oxygen
- Carbon disulfide
- Organic solvents
- Bromide
- Methyl chloride
- Heavy metals
 - Lead
 - Arsenic
 - Mercury
 - Bismuth
 - Thallium
 - Tin
- Environmental toxins
 - Plants and mushrooms
 - Venom (e.g., snakes, insects, fish)
- Inhalants
 - Gasoline
 - Glue
 - Ether
 - Nitrous oxide
 - Nitrates
- Illicit drugs
 - Cocaine
 - Heroin
 - Benzodiazepines
 - Lysergic Acid Diethylamide (LSD)
 - Phencyclidine (PCP)
- Withdrawal syndromes
 - Alcohol
 - ◇ Mild: Tremors, irritability, anorexia and nausea
 - Symptoms usually appear within a few hours after reduction or cessation of alcohol intake, and tend to resolve within 48 h
 - Symptoms may include dysphoria, insomnia, diaphoresis, impaired attention and concentration, tremors, and seizures
 - Tend to occur 1–10 d after cessation of benzodiazepines, may last several days to weeks

- ◇ Severe: “delirium tremens”—carries significant mortality
 - Tremulousness, hallucinations, agitation, confusion, disorientation, and autonomic hyperactivity (fever, tachycardia, and diaphoresis) typically occur 72–96 h after cessation of drinking
 - Symptoms generally resolve within 3–5 d.
- ◇ Alcohol withdrawal seizures: typically one or a few brief generalized convulsions
 - Occur 12–48 h after cessation of alcohol intake
 - Antiepileptic drugs are not indicated for typical alcohol withdrawal seizures
 - Other causes for seizures must be excluded
- ◇ Secondary derangements: patients with alcohol withdrawal are susceptible to hypomagnesemia, hypokalemia, hypoglycemia, and fluid losses, mostly as a result of fever, diaphoresis, and vomiting
- ◇ If hypoglycemia is present, thiamine should be administered before glucose to prevent precipitation of Wernicke’s encephalopathy
- ◇ Treatment
 - Chlordiazepoxide: 100 mg iv or PO q2–6 h as needed; Maximum dose: 500 mg in the first 24-h period. The initial 24-h dose can be administered again over the next 24 h, then the dosage can be reduced by 25–50mg per day each day thereafter
 - Lorazepam or other longer lasting benzodiazepines may facilitate smoother symptomatic control. Can be given 1–2 mg PO or IV q6–8 h as needed
 - Oxazepam 15–30 mg PO, q6–8 h as needed can be given to patients with hepatic failure, as it is excreted by the kidneys
 - Effective use of propofol drip has been reported.
 - Maintenance of fluid and electrolyte balance is important
 - Haloperidol should be avoided as it may cause paradoxical agitation
- Nicotine withdrawal
 - ◇ Signs and symptoms include bradycardia, depressed mood, anxiety, irritability, slowed cognition, sleep disruption, difficulty concentrating, increased appetite, and impatience

- ◊ Nicotine craving is most prominent within the first three days, and irritability, anxiety, and disturbed sleep peak at about 1 wk
- ◊ Treatment: 21 mg transdermal nicotine patch—anecdotal use in neurocritical care setting have not shown serious side effects
- ◆ Metabolic
 - Fluid disturbances
 - Dehydration: diabetes insipidus (DI), inadequate fluid administration
 - Water intoxication: psychogenic polydipsia, iatrogenic
 - Electrolyte disturbances
 - Hyponatremia
 - Causes: edematous states (CHF, nephritic syndrome, cirrhosis), endocrine dysfunction (hypothyroidism, adrenal insufficiency), iatrogenic (postoperative fluid overload, medication-induced, hypotonic fluid administration), SIADH, “cerebral salt wasting”
 - ◊ Post-op patients are at relatively high risk owing to stress, nausea, volume contraction, and medications
 - ◊ SIADH is a major cause in patients with CNS disease (brain abscess or infection, brain tumor, head trauma, etc.)
 - Treatment is by fluid restriction, unless the patient has vasospasm following subarachnoid hemorrhage, then hypertonic saline administration may be required
 - ◊ Centrally mediated renal sodium wasting (cerebral salt wasting)—existence of this syndrome is controversial
 - Results in cellular swelling and brain edema
 - Symptoms: weakness, confusion, disorientation, seizures, and coma
 - ◊ Rapidity of development is an important determinant of symptoms
 - Treatment
 - ◊ Can be conservative if hyponatremia developed gradually (also, often less symptomatic)
 - ◊ Balance risk of damage from hyponatremia vs risk of damage from central pontine myelinolysis
 - Hypernatremia
 - Causes: extrarenal (insensible losses owing to fever, burns, mechanical ventilation, diarrhea, and sweat), renal

- (osmotic diuresis, central DI, nephrogenic DI), iatrogenic (hypertonic saline administration, medications)
 - ◊ Typically will not develop if thirst mechanisms are intact and if there is unrestricted access and ability to drink water
 - Hyperosmolar state causes brain cells to shrink—brain equilibrates to these in several hours, therefore these states should be corrected slowly
 - Symptoms: agitation, seizures, lethargy, coma, and seizures; intracranial bleeding can develop as the shrinking brain pulls away from the meninges and bridging veins tear
- Glucose
 - Hypoglycemia
 - Confusion, seizures, stupor, coma, and occasionally hemiparesis or other focal neurologic findings
 - Typically caused by accidental or deliberate overdoses of insulin or antidiabetic agents, insulin-secreting islet cell tumors or retroperitoneal sarcoma, protracted ethanol intoxication (in rare cases)
 - Initial symptoms consist of nervousness, hunger, tachycardia, palpitations, anxiety, sweating, and tremor
 - ◊ Frequently recognized by the patient and respond quickly to oral or parenteral glucose
 - If the syndrome progresses, patients develop increasing confusion, drowsiness, motor restlessness, myoclonic twitching, and seizures
 - Hyperglycemia
 - Ketotic or non-ketotic
 - May lead to encephalopathy or coma
- Calcium: hypocalcemia, hypercalcemia
- Magnesium: hypomagnesemia, hypermagnesemia
- Respiratory
 - Hypoxia
 - Hypercapnia
 - Caused by underlying pulmonary disease or narcotic administration
 - CO₂ retention can cause headache, papilledema, and altered levels of consciousness
 - EEG frequently shows slowing in the theta and delta ranges
 - Hypercapnia usually does not cause prolonged coma or irreversible brain damage

- Treatment
 - ◇ Intermittent positive pressure ventilation
 - ◇ Oxygen can be dangerous because it may blunt the respiratory drive but should be administered to raise arterial oxygen tension to between 50 and 55 mmHg
 - Pulmonary embolus
- Infectious
 - Septic encephalopathy can be a result of any infections other than primary CNS infections
 - Symptoms may be owing to widespread multiorgan injury associated with the systemic inflammatory response
 - Causes of septic encephalopathy
 - Bacteremia/sepsis
 - Urinary tract infection/urosepsis
 - Pneumonia
 - Peritonitis
 - Bacterial endocarditis
- Gastrointestinal
 - Hepatic encephalopathy
 - Caused by cirrhosis of any cause, can be triggered or exacerbated by GI bleeding
 - EEG abnormalities can include bilaterally synchronous δ -waves, that are frequently biphasic
 - Asterixis: lapses of sustained muscle contraction.
Can occur with other metabolic encephalopathies as well (including hypercapnia)
 - Magnetic resonance imaging (MRI) can show diffuse cerebral edema
 - Ammonia levels are often elevated
 - Liver function tests can be high, low or normal
 - Coagulopathy can result
 - Treatment
 - ◇ Prevent elevated ammonia concentrations
 - ◇ Dietary restrictions of protein
 - ◇ Antibiotics (such as neomycin) to suppress or eliminate urease-producing bowel bacteria
 - ◇ Lactulose from 30 to 50 mL PO/rectally qd to qid
 - ◇ Liver transplant has been successful in reversing encephalopathy and even coma
 - Pancreatic insufficiency
- Renal failure leading to uremia

- Endocrine causes
 - Thyroid disease
 - Hypothyroidism
 - ◇ “Myxedema coma”: obtundation, nonpitting edema, hypothermia, hypoventilation, hypotension, and hypoglycemia
 - ◇ Treated with thyroid replacement with cardiovascular and pulmonary support; adrenal insufficiency may coexist
 - Hyperthyroidism
 - ◇ Encephalopathy, hyperdynamic cardiac function (tachycardia, increased cardiac output and ejection fraction), decreased vascular resistance, arrhythmias (afib, SVT), pulmonary compromise, and fever
 - ◇ If suspected, therapy should be started immediately. Close monitoring, cardiovascular/pulmonary/fluid support, and rapid administration of antithyroid drugs and β -blockers
 - Acute adrenal failure
 - Addisonian crisis from pituitary tumors, primary adrenal disease, adrenal suppression from chronic steroid therapy or rapid cessation of steroids
 - Symptoms: obtundation with hyponatremia and hyperkalemia
 - May follow infection, injury or surgery
 - Diagnosis can be confirmed by random cortisol levels below 20 $\mu\text{g/dL}$; if in doubt, a cosyntropin stimulation test may be required
 - Treatment: 100mg IV hydrocortisone followed by a 75–100 mg dose every 6 h, followed by an oral taper
 - ◇ If planning a cosyntropin test but immediate treatment is needed, give dexamethasone 4 mg iv every 4 h instead of hydrocortisone, as dexamethasone will not interfere with the measurement of endogenous cortisol levels; when the test is complete, the patient can be tapered to hydrocortisone
 - Hypopituitarism
 - Addison’s disease
 - Cushing’s disease
 - Parathyroid disorders
 - Hypoparathyroid
 - Hyperparathyroid

- Porphyria
- Nutritional
 - Vitamin deficiency
 - Thiamine
 - ◇ Wernicke's encephalopathy
 - ◇ Ophthalmoplegia, ataxia, global confusion
 - ◇ Treatment: immediate administration of thiamine 50–100 mg IV or IM. This dose should be repeated daily until the patient resumes a normal diet and should be given before glucose-containing solutions
 - ◇ Korsakoff's psychosis
 - B₁₂ deficiency
 - Folate deficiency
 - Pyridoxine deficiency
 - Nicotinic acid deficiency
 - Hypervitaminosis: A and D
- Body temperature: hypothermia, hyperthermia
- Acid-base disorders
- Cardiac: Arrhythmia
- Errors of metabolism
 - Wilson's disease

Key Points

- ◆ Encephalopathy usually presents with nonfocal neurological exam as a result of diffuse cerebral disturbance
- ◆ Common and reversible etiologies should be investigated first (electrolytes, glucose, hypoxia, infection)
- ◆ Toxic and withdrawal syndromes occur commonly

Suggested Reading

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