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 25–50 mg 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 subaracnoid hemorrhage, then hypertonic saline administration may be required
    - Centrally mediated renal sodium wasting (cerebral salt wasting)—existence of this syndrome is controversial
  - Hypernatremia
    - Causes: extrarenal (insensible losses owing to fever, burns, mechanical ventilation, diarrhea, and sweat), renal

Encephalopathy

- Encephalopathy
  - 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

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    - Hypernatremia
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(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 µg/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
Encephalopathy

- Porphyria
- Nutritional
  - Vitamin deficiency
    - Thiamine
      - Wernicke’s encephalopathy
      - Ophthalmoplegia, ataxia, global confusion
      - Treatment: immediate administration of thiamine
        50–100 mg IV or IV. 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
American Psychiatric Association. Diagnostic and Statistical Manual of
Association; 1994:123–133.
Aminoff MJ, ed. Neurology and General Medicine, 3rd edition. Philadel-
1053–1067.
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Handbook of Neurocritical Care
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