Encephalopathy: Types, Causes, Symptoms, and Treatment

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LECOM Primary Care Conference 2020
Saturday, March 7, 2020 – 7:30 AM

Disclosures

☐ I have nothing to disclose.
Objectives

- At the end of this lecture, one should be able to:
  - 1. Discuss the different types of encephalopathy
  - 2. Compare and contrast delirium and dementia
  - 3. Discuss the many causes of encephalopathy
  - 4. Discuss the symptoms of encephalopathy
  - 5. Discuss the treatment of encephalopathy

References

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References

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- https://www.sciencedirect.com/topics/neuroscience/delirium-tremens

Encephalopathy Definition

- Quoted from The Oxford Dictionary,
  - “A disease in which the functioning of the brain is affected by some agent or condition.”
Encephalopathy Definition

- Quoted directly from the National Institute of Neurological Disorders and Stroke:
  - "Encephalopathy is a term for any diffuse disease of the brain that alters brain function or structure. Encephalopathy may be caused by infectious agent (bacteria, virus, or prion), metabolic or mitochondrial dysfunction, brain tumor or increased pressure in the skull, prolonged exposure to toxic elements (including solvents, drugs, radiation, paints, industrial chemicals, and certain metals), chronic progressive trauma, poor nutrition, or lack of oxygen or blood flow to the brain.

- The hallmark of encephalopathy is an altered mental state.

- Depending on the type and severity of encephalopathy, common neurological symptoms are progressive loss of memory and cognitive ability, subtle personality changes, inability to concentrate, lethargy, and progressive loss of consciousness. Other neurological symptoms may include myoclonus (involuntary twitching of a muscle or group of muscles), nystagmus (rapid, involuntary eye movement), tremor, muscle atrophy and weakness, dementia, seizures, and loss of ability to swallow or speak. Blood tests, spinal fluid examination, imaging studies, electroencephalograms, and similar diagnostic studies may be used to differentiate the various causes of encephalopathy."

Remember, most encephalopathies are caused by diseases that occur outside of the brain.
Common Synonyms for Encephalopathy

- Delirium
- Mental status changes
- Altered mental status
- Confusion
- Disorientation
- Acute confusional state
- Transient alteration of awareness

Acute and Chronic Encephalopathies

- Most of the time when we think of encephalopathies, we think of acute encephalopathies, mainly because there is an acute change in a patient seen by family, friends, nursing, etc.
- Chronic encephalopathies exist too, often in the form of exacerbated chronic encephalopathies, such as, temporarily worsened Alzheimer Dementia.
Confusion Assessment Method (CAM)

Table 6: Confusion Assessment Method (CAM) Diagnostic Algorithm

1) Acute onset and fluctuating course
2) Inattention, distractibility
3) Disorganized thinking, illogical or unclear ideas
4) Alteration in consciousness

The diagnosis of delirium requires the presence of both features 1 AND 2, plus EITHER feature 3 or 4.


Delirium

- The condition that is most often associated with encephalopathy is delirium.
- Delirium has many causes.
- The mainstay of treatment or therapy is to treat the underlying cause of the delirium, and the delirium will resolve.
Delirium

- Acute, transient, potentially reversible confusional state
- Occurs in 30 to 50% of patients admitted to a hospital over age of 69
- The prevalence of delirium at hospital admission ranges from 14% to 24%
- The incidence of delirium during hospitalization ranges from 6% to 56% in general hospital populations
- At any one time 10% of patients will be delirious
- It is often the presenting symptom of an illness in the elderly

Features

- Fluctuating
- Clouded consciousness
- Reduced awareness
- Impaired attention
- Incoherent
- Restlessness
- Illusion
- Hallucination
- Disturbed sleep wake cycles
Etiology

- Primary cerebral
- Systemic
- Exogenous substances
- Withdrawal
- Psychiatric illnesses mistaken as delirium

Primary Cerebral

- Seizure – non-convulsive status epilepticus, status epilepticus, post-ictal state, Todd’s Paralysis
- Ischemic – hypoxic, anoxic, TIA, stroke
- Infection -meningitis, encephalitis, abscess, cysticercosis
- Neoplasm – both primary and metastatic
- Trauma – concussion (mTBI), TBI, diffuse axonal injury, ICH, post-concussive syndrome, Chronic Traumatic Encephalopathy (CTE)
- Hydrocephalus, Normal Pressure Hydrocephalus (NPH)
Systemic Disorders

- Infection - pneumonia, urinary tract infection, sepsis
- Metabolic – glucose changes, electrolyte disturbances, uremia, hepatic failure, vitamin disturbances, dehydration
- Endocrine – thyroid disorders
- Cardiovascular - congestive heart failure, myocardial infarction, HTN
- Collagen vascular disease/Connective tissue disease - "fibro fog," lupus

Exogenous Substances

- Medications
  - Sedatives – benzos for mood
  - Narcotics – chronic opiates for pain
  - Others – chemo, steroids, statins, anticholinergics, anticonvulsants, hypnotics, Parkinson’s Disease (PD) meds, antihistamines
- Anesthesia – age and obesity are factors
- Poisons/Heavy metals – need to ask about and check for them.
  - Ask about well water
  - Does a family member work in the plating industry, access to arsenic?
  - How much sushi or fish does one eat?
- Recreational drugs
  - With marijuana now being medically legal, we are seeing more patients that are constantly intoxicated from it.
    - Because they can walk, talk, and even drive while "high," most patients do not think it affects their memory, cognition, or behavior
    - Cyclic vomiting syndrome
Withdrawal

- Alcohol
  - Many alcoholics are more confused when they are withdrawing from alcohol vs intoxicated – state of mind mental status.

- Sedatives/Benzos
  - Benzo withdrawal is very difficult for a lot of patients, and it can take weeks, months, and even years for some patients to recover from it; those who were on high doses for many years.

Psychiatric Illnesses Mistaken as Delirium

- Delirium is often misdiagnosed as depression.
  - Both have decreased attention and concentration
  - Both have insomnia
  - Depression is dysphoric
  - Delirium typically fluctuates more
- Mania can appear like an agitated and hyperactive delirium where there are delusions and psychosis.
- Schizophrenia, mania, and depression, usually have a history to them; they are not something new, which is typically the case in delirium.
Workup

- History and physical
  - Review medications
  - Review old records; hospital and outpatient
  - Ask about travel
  - Family history of dementia, early onset dementia?
- Labs – CMP, electrolytes, glucose, CBC, BUN, creatinine, calcium, ammonia, TFTs, B vitamin levels, urinalysis, RPR, methylmalonic acid level, Lyme’s screen with reflex, ANA, blood cultures, ammonia
- Pulse oximetry/ABG
- Chest X-ray
- Electroencephalogram (EEG)
- CT Head, Brain MRI, both with and without contrast
- Spinal tap – with CSF opening and closing pressures, CSF labs, CSF gram stain and fungal stains, CSF cultures.

Treatment

- Eliminate or correct underlying etiology
- Environmental modifications
  - Clock
  - Calendar
  - Lighting
  - ACE Units – Acute Care for Elders – have helped reduce encephalopathy and delirium in the hospital setting.
- Medications
  - Haloperidol – can build up in the system, especially in elderly and obese patients, and it can cause a delirium/encephalopathy
  - Benzodiazepine – can cause a delirium/encephalopathy but it can be reversed with flumazenil.
Preventable Delirium

- Because alcoholism is such a common, devastating, expensive, lethal, and preventable delirium/encephalopathy, I would like to spend some time discussing this cause of delirium.
- Because alcoholism is so common, it's often just one cause of delirium in patients with a multifactorial encephalopathy.
- You need to ask about drug and alcohol use in all patients being worked up for delirium because even though they are causes of delirium, they can also worsen and complicate the work up and treatment.

Alcoholism

- Problem drinkers in the United States
  - 6.2% of adults
    - 8.4% are men.
    - 4.2% are women.
  - 4.3 million adolescents (12 to 20 yo) reported binge drinking (5 drinks for men/4 drinks for women) at least once in the past month.
- 88k alcohol related deaths per year in the U.S.
  - Third leading cause of preventable death in the U.S. Tobacco is #1 and poor diet/decreased exercise is #2.
- In 2010, alcohol misuse cost the U.S. $249 billion
  - 75% of that price is secondary to binge drinking.
Alcoholism

- Direct effects
  - intoxication
  - addiction
  - withdrawal

- Indirect effects
  - Nutritional – depletes most B vitamins and drinking empty calories leading to malnutrition.
  - Related diseases – cirrhosis, alcoholic dementia, vitamin B12 deficiency, thiamine deficiency (beriberi), etc.

Symptoms Correlating with Blood Alcohol Levels (mg/dL)

- 50-150
  - Euphoria, shyness, impaired concentration and judgement

- 150-250
  - Slurred speech, ataxia, anger, diplopia, labile mood, drowsiness

- 300
  - Stupor with combativeness

- 400
  - Coma

- 500
  - Respiratory paralysis
Ethanol Withdrawal

- Tremor, insomnia, agitation, increased sympathetic activity
- Hallucinations, nightmares, illusions, formication
- Nausea and vomiting
- Seizures occur within 48 hours of withdrawal (rum fits)

Ethanol Withdrawal (continued)

- Diagnosis
  - History and physical
  - Ethanol level is low or zero
- Treatment
  - CIWA Protocol
  - Sedation – phenobarbital, benzos
  - Correct electrolytes and glucose
  - Vitamins and nutrition
    - Thiamine before glucose to prevent progression into Wernicke's Encephalopathy – study in 2012 proved this is not true.
    - [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556948/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556948/)
Delirium Tremens (DT)

- Occur 48-72 hours after last drink
- Usually follows seizures
- If a seizure occurs during the DTs, think of another cause.

Delirium Tremens (DT)

- Lasts hours to a few days
- Similar to withdrawal but more intense
- Fever, tachycardia, sweating
- Mortality is 5 to 15% without treatment
  - Shock
  - Pneumonia
  - Cirrhosis
Delirium Tremens (DT)

- **Diagnosis**
  - History and physical
  - Imaging
  - Lab tests

- **Treatment**
  - Prevention
  - Sedation – CIWA Protocol
    - Phenobarbital
    - Benzodiazepine
  - Fluids, electrolytes, glucose
  - Nutrition, vitamins
  - Treat associated conditions – shock, aspiration pneumonia, etc.
Wernicke Encephalopathy

- Most often alcohol related but can be caused by extreme malnutrition
- Thiamine deficiency
- Diffuse axonal, neuronal and myelin loss
- Petechial hemorrhages
- Global confusion, impaired memory, inattentiveness
- Abnormal eye movements - nystagmus, lateral rectus palsy or ophthalmoplegia
- Ataxia - truncal, limb, dysarthria

Diagnosis

- History and physical
- Transketolase deficiency – studies have shown that thiamine deficiency leads to Wernicke–Korsakoff syndrome only in those whose transketolase has a reduced affinity for thiamine.

Treatment

- Parenteral thiamine
Prognosis

- 100% fatal without treatment
- 10% fatal with treatment
- 35% left with nystagmus
- 60% left with mental deficiencies

Korsakoff Psychosis

- Emerges as Wernicke Encephalopathy clears
- Amnesia - retrograde and anterograde
- Confabulation, impaired insight
- Lesion in the dorsal medial nucleus of the thalamus or mamillary bodies
- Usually memory deficits remain despite treatment
Alcohol Related Complications

- Cerebellar degeneration
- Amblyopia
- Peripheral neuropathy
- Myopathy
- Dementia – Alcoholic Dementia

Hepatic Encephalopathy

- Seen in cases of chronic hepatic insufficiency or portacaval shunting
- Cause is from elevated blood ammonia levels
Pathogenesis

- Many theories for the cause of hepatic encephalopathy
  - Neurotoxins are no longer cleared by the liver and they affect the astrocytes, which account for 75% of the brain tissue.
    - Ammonia – delirium caused from too much ammonia does not cause EEG changes (triphasic waves) as seen in hepatic encephalopathy
  - Manganese
  - In cirrhosis and acute liver failure, astrocytes have been shown to swell, causing cerebral edema and increased ICP
  - Too much GABA. GABA is a down-regulator in the brain and this theory believes that is up-regulated in cirrhosis, leading to decreased function in the brain.
    - Studies have shown that some patients with hepatic encephalopathy respond to flumazenil (benzo reversal agent, benzos are gabanergic), and their hepatic encephalopathy improves.

Clinical Features

- Delirium, coma, asterixis, rigidity, upper motor neuron signs, frontal release signs
- May remain mild or progress to death
Clinical Features (continued)

- Stages
  - I  Euphoria, confusion, sleep disorder
  - II Lethargy, confusion, asterixis
  - III Marked confusion, slurred speech, sleepy
  - IV Coma

Treatment

- Eliminate underlying cause if possible
  - Example: valproic acid
- Reduce serum ammonia
  - Limit protein
  - Cleanse colon
    - Lactulose
    - Neomycin – reduces ammonia producing bacteria in the colon
Dementia

“Dementia is not a specific disease. It's an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities.” – Alzheimer’s Association, www.alz.org.

Alzheimer Disease

- Progressive, degenerative brain disease characterized by memory loss and loss of other cognitive function
- Changes in behavior, personality, judgement and ADLs
- Most common dementia over age 65
  - As of 2018, 1 in 10 seniors age 65+ has Alzheimer's dementia
- Risk factors include: Down’s syndrome, family history and advanced age
- As of 2018, an estimated 5.7 million Americans have some form of dementia and other memory disorders.
Relative Frequency of Dementia

- Alzheimer dementia: 52%
- Multi-infarct dementia (MID): 17%
- Combined Alzheimer and MID: 14%
- Parkinson disease: 2%
- Psychiatric: 1%
- Unknown: 7%
- Other brain problems: tumor, degenerative, infectious: 7%

Economic Burden

- In 2018, dementia treatment cost $277 billion in the U.S.
- It's now the most expensive disease
- In 2018, the lifetime dementia cost for a family was $341,840
Genetic Research

- Linked to chromosomes 1, 14, 19 and 21
- Early onset 1, 14 and 21
- Late onset 19 - most common
  - ApoE4 gene
    - Dr. Crystal, Cornell University, is developing gene therapy that is designed to replace the APOE4 gene with APOE2 (shown to be protective against Alzheimer Dementia)
  - Beta-secretase (beta-site amyloid precursor protein-cleaving enzyme) may play a significant role in the disease

Cholinergic Hypothesis

- Acetylcholine is important to the hippocampus, cerebral cortex and amygdala
- Alzheimer brains have marked decrease in concentrations of acetylcholine
- Replacement may help with cognitive function
CLINICAL PRESENTATION

- Memory impairment
- Word-finding difficulties
- Difficulty performing complex tasks (e.g., keeping checkbook, cooking)
- Geographic or temporal disorientation
- Day-night disorientation
- Language deterioration (e.g., empty speech)
- Difficulties with simple chores
- Troublesome behavior including:
  - Wandering
  - Irritability
- Depression
- Hallucinations, delusions
- Agitation
- Incontinence
- Total dependence on caregivers

DIFFERENTIAL DIAGNOSIS

- Causes of dementia can include:
  - Vascular disease (including multi-infarct dementia)
  - Parkinson's disease
  - Pick's disease
  - Huntington's disease
  - Normal pressure hydrocephalus
  - Metabolic disorders, including Vitamin B₁₂ deficiency, chronic drug intoxication, hypothyroidism, and alcoholism
  - Infectious causes, including HIV, neurosyphilis, and bacterial meningitis
  - Major depression

- The clinical diagnosis of Alzheimer's disease can be made with 85% to 90% accuracy.
Diagnosis

- History and physical
- Imaging - MRI, CT Scan, SPECT, PET
- Electroencephalogram
- Spinal tap
- Laboratory tests - RPR, thyroid function, B12 level, HIV, metabolic profile
- Neuropsychological testing
Progression of Alzheimer's

- **Mild Cognitive Impairment**
  - Duration: 7 years
  - Disease begins in Medial Temporal Lobe
  - Symptoms: Short-term memory loss

- **Mild Alzheimer's**
  - Duration: 2 years
  - Disease spreads to Lateral Temporal & Parietal Lobes
  - Symptoms include: Reading problems, Poor object recognition, Poor direction sense

- **Moderate Alzheimer's**
  - Duration: 2 years
  - Disease spreads to Frontal Lobe
  - Symptoms include: Poor judgment, Impulsivity, Short attention

- **Severe Alzheimer's**
  - Duration: 3 years
  - Disease spreads to Occipital Lobe
  - Symptoms include: Visual problems

Management

- Non-pharmacological
- Medications for Alzheimer dementia
  - donepezil
  - tacrine
  - rivastigmine
  - galantamine
  - memantine
- Medications for behavior
  - benzodiazepine
  - haloperidol
- Support services
Behavioral Symptoms of Alzheimer Dementia

- Agitation
- Delusions
- Depression
- Anxiety
- Insomnia
- Hallucinations

Sundowning

- Increased behavior problems
- Evening phenomenon
- Decreased sensory input
- Managed by reorienting the patient and increase lighting
- May need medication
Non-pharmacological Management

- Simple instructions
- React calmly
- Avoid confrontations
- Try to maintain familiar environments
- Family support

Impact of Dementia on Patient

- Falls
- Hygiene - personal and dental
- Safety hazards
- Driving problems
- Money management problems
- Lack of exercise
- Incontinence
Causes of death in Alzheimer Dementia

- Complications of dementia 68%
  - Pneumonia (54%)
- Stroke 9.3%
- Cardiovascular disease 3.5%
- Cancer 2.3%
- Other 16.9%

Caregiver Burden

- Caregivers spend 69-100 hours per week providing care
- Caregivers suffer from:
  - More doctor visits
  - More prescription drugs
  - More likely to be hospitalized
  - More likely to be clinically depressed
Caregiver Support and Information

- Encourage independence without sacrificing security
- Assist patient only when needed
- Learn to compromise
- Share activities
- Support network
- Educate themselves

Caregiver Support and Information (continued)

- Counseling
- Social support
- Community groups
- Training in behavior management
Irreversible Dementias

- Vascular
- Demyelinating
- Degenerative
- Neoplastic
- Trauma
- Infections
- Toxic/Metabolic

Reversible Dementia

- Syphilis
- Hypothyroidism
- B12 deficiency & other vitamin deficiencies
- Normal pressure hydrocephalus
- Tumor
Multi-infarct Dementia

- Stepwise course of memory decline
- Focal signs and symptoms
- Abnormal MRI or CT Scan

Pick Disease

- Rare
- Woman more than men are affected
- Severe atrophy of frontal and temporal lobes
- Symptoms similar to SDAT
- Abulia, apathy, frontal release signs, speech and language disturbance
- No treatment
Hydrocephalus

- Characterized by increased CSF volume and dilated ventricles

Normal Pressure Hydrocephalus

- Treatable dementia
- Often follows trauma, subarachnoid hemorrhage or meningitis
- Triad: dementia, incontinence, ataxic (apraxic) gait
- No headache or signs of increased intracranial pressure
- Spasticity, hyperreflexia, pathologic reflexes
Normal Pressure Hydrocephalus

- **Diagnosis**
  - History and physical
  - MRI or CT Scan
  - Indium cisternogram

- **Treatment**
  - Shunt

- **Prognosis**
  - Can be predicted with lumbar puncture
  - Sixty percent may improve with shunt
  - Better outcome if gait is primarily affected
  - Better outcome if found and treated within 6 months to a year of onset.

Obstructive Hydrocephalus

- Congenital
- Postinflammatory
- Posthemorrhage
- Mass
Communicating Hydrocephalus

- Increased CSF production
- Defective absorption of CSF
- Impaired venous drainage

Hydrocephalus Ex Vacuo

- Hydrocephalus due to loss or atrophy of brain tissue
- Not due to increased CSF pressure.
Clinical Features of Hydrocephalus

- **Children**
  - Enlargement of sutures and fontanelles, Parinaud syndrome, impaired motor and intellectual development, sixth nerve palsies

- **Adults**
  - Headache, lethargy, weakness, incoordination, dementia, papilledema, ataxia, long tract signs

Hydrocephalus

- **Diagnosis**
  - H&P
  - Imaging

- **Treatment**
  - Underlying cause
  - Shunt

- **Prognosis**
  - Depends on etiology
  - Untreated infant mortality
    - 50% at 1 year of age
    - 75% at 10 years of age
Stroke and TIA

- Strokes and TIAs often present with focal neurological deficits, including aphasia; in large, left brain dominant, left MCA strokes.
  - In smaller, left brain dominant, right MCA strokes, patients can have speech problems with intonation, tone, stress, and rhythm (prosody), loss of self-awareness (anosognosia), and neglecting of one's body (asomatognosia).
    - These symptoms can present like a delirium.
  - In ACA strokes, patients can have an absence of willpower or an inability to act decisively (abulia), disinhibition, decreased or loss of executive dysfunction, and they won't move or speak (akinetic mutism).
    - These symptoms can present like a delirium.

- In addition to contralateral sensory loss, thalamic strokes can cause aphasia (if dominant side involvement), executive dysfunction, decreased level of consciousness, and memory impairment.
  - These symptoms can present like a delirium.
**Stroke and TIA**

- Fortunately, when patient's present with a stroke or TIA caused encephalopathy/delirium, it's typically an odd presentation.
  - There may be no risk factors or obvious causes for the delirium.
  - They cannot express themselves in speaking but they can write down answers appropriately.
  - Sometimes the aphasia, decreased self-awareness, and decreased executive dysfunction prevents the patient from recognizing something is wrong with them.

- If there is a suspicion for a stroke-induced delirium, then I suggest ordering a Brain MRI, without contrast, looking for that stroke on DWI.
  - Most studies show that an acute stroke will show up on a Brain MRI if it occurred within the last 14 to 16 days.
  - In obese, claustrophobic, and/or pacemaker patients, you may need to perform 2 Head CTs, without contrast, in order to image the stroke.
Stroke and TIA

- If an acute or subacute stroke is found on imaging, then perform a stroke work up and treat it.
- A speech pathologist referral can also help with ascertaining aphasia and cognitive problems and they can help with rehab.
- Recurrent strokes can lead to a vascular and multi-infarct dementia.

Questions?