Amnestic Disorders

Introduction

- Amnesia - deficit in memory caused by brain damage, disease, or psychological trauma, which can be either wholly or partially depending upon the extent of damage caused
- Disorder of cognitive function - memory and learning are out of proportion to components of mentation and behavior
- Originally defined by Ribot
- Term amnesia is from Greek, meaning "forgetfulness"; from ἀ- *(a-)*, meaning "without", and μνήσις *(mnesis)*, meaning "memory“

Definition

- DSM-IV-TR: 4 diagnostic entities under this category:
  1. Amnestic disorder due to cerebral or systemic medical condition
  2. Substance-induced amnestic disorder
  3. Amnestic disorder due to unknown etiology
  4. Amnestic disorder not otherwise specified.
- DSM-5: All categories covered under mild and major neurocognitive disorder
- ICD-10: “Organic amnestic syndrome, not induced by alcohol and other psychoactive substances.”
- For substance-induced amnestic disorder, ICD-10 uses the term “Amnestic syndrome.”

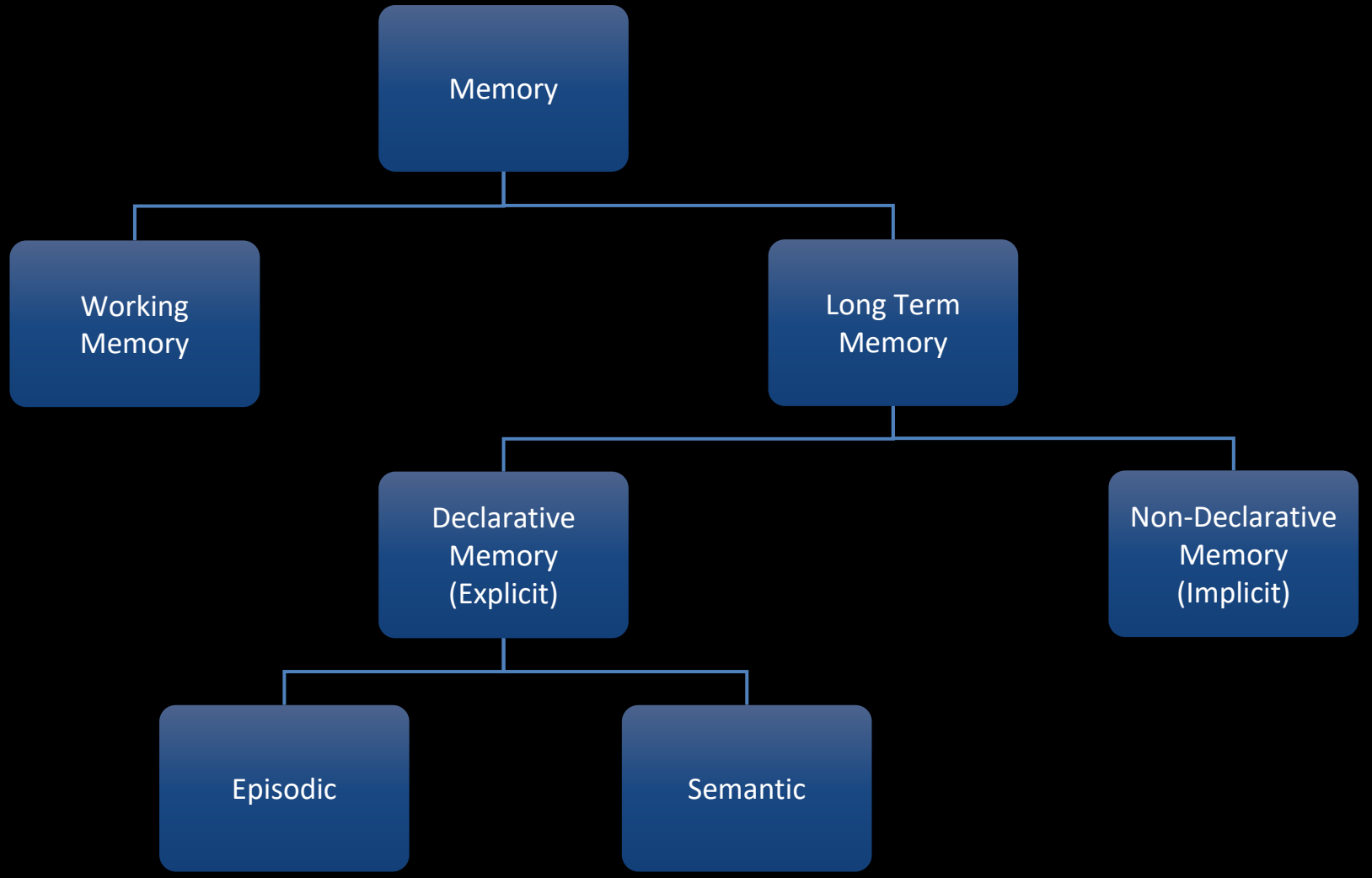
ICD-10 Research Criteria for Organic Amnestic Syndrome

A. Memory impairment manifest by both:
   1. a defect of recent memory (impaired learning of new material), to a degree sufficient to interfere with daily living
   2. a reduced ability to recall past events

B. Absence of:
   1. a defect in immediate recall (as tested, for example, by the digit span)
   2. clouding of consciousness and disturbance of attention, as defined in Delirium
   3. global intellectual decline (dementia)

C. Objective evidence (physical and neurological examination, laboratory tests) and/or history of an insult to or a disease of the brain (especially involving bilaterally the diencephalic and medial temporal structures but other than alcoholic encephalopathy) that can reasonably be presumed to be responsible for the clinical manifestations described under A

Types of Memory



Types of Memory

Working Memory

- Ability to temporarily store & process information online.
- Very flexible
- Capacity to store is limited
- Decays rapidly

Long Term Memory

- Information stored will remain for an indefinite time
- No known limit of capacity
- Information is organized
- Information retrieved from LTM by retrieval cues

Types of Long Term Memory

Declarative Memory (Explicit)

- Allows long term representation & reproduction of the past
- Not a permanent record
- Conscious recollection of episodes and facts

Non-Declarative Memory (Implicit)

- Previous experience facilitates performance without conscious awareness

Types of Declarative Memory

Episodic Memory

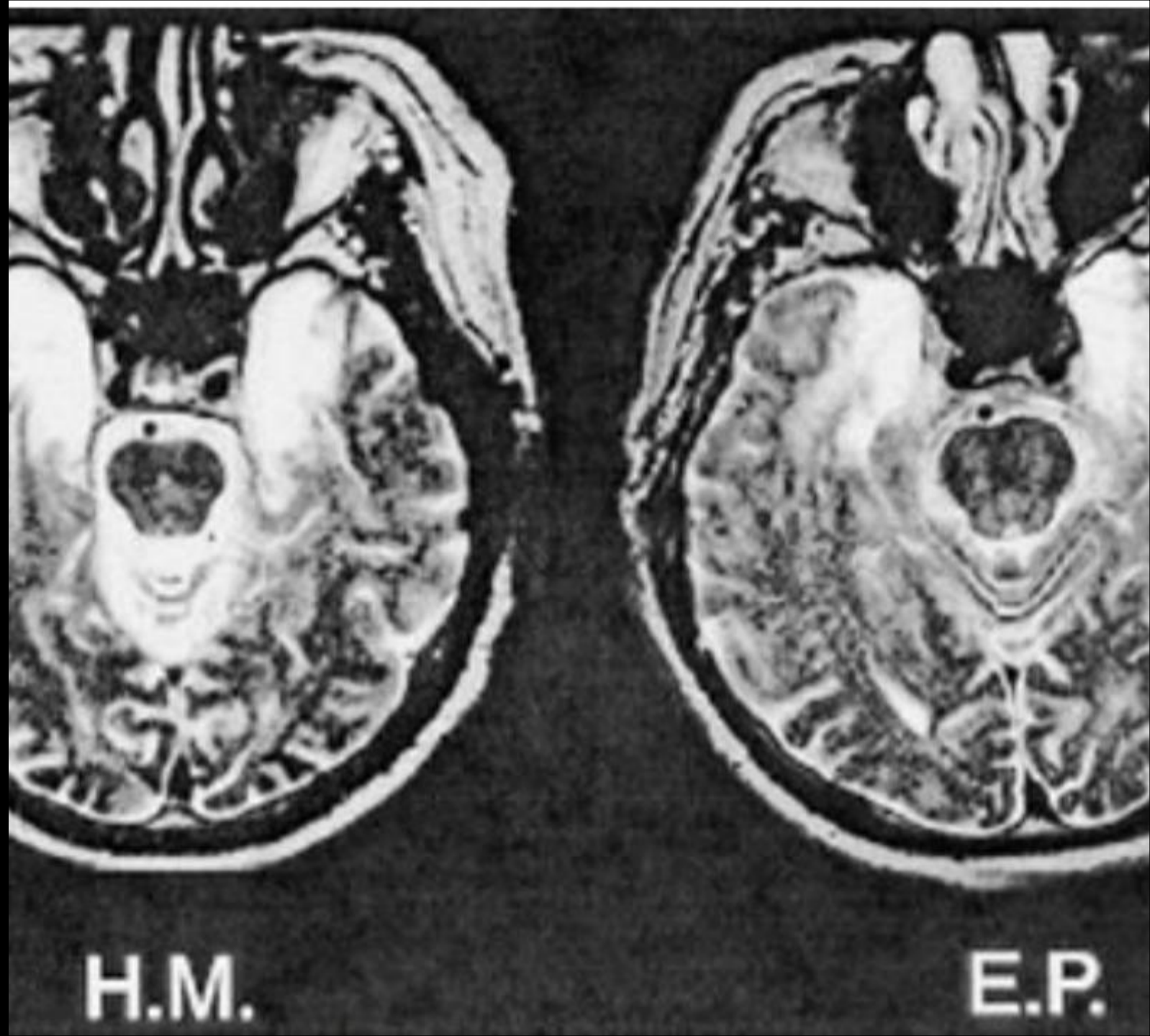
- Memory of specific episodes

Semantic Memory

- Memory of facts, principles and rules
- Evolved from episodic memory

Historical Perspective

- 1950s - Scoville and Milner described the case of bilateral removal of medial temporal lobes, followed by profound anterograde amnesia (the “H.M.” case).



Historical Perspective

- Henry Molaison - partial seizures + tonic-clonic seizures
- 1953 - Dr. Scoville localized Molaison's epilepsy to left & right medial temporal lobes and resected them, including the removal of hippocampal formation, most of the amygdaloid complex and entorhinal cortex
- Epilepsy was controlled but Molaison developed:
  - Severe anterograde amnesia: working memory and procedural memory were intact - could not commit new events to his explicit memory.
  - Moderate retrograde amnesia: could not remember most events preceding 1-2 years before surgery, nor some events up to 11 years before - amnesia was temporally graded.
- His ability to form long-term procedural memories was intact; thus he could learn new motor skills, despite not being able to remember learning them.

Epidemiology

- Data regarding overall prevalence of amnestic disorders is lacking.
- Alcohol abuse and head trauma appear to be the two most common causes of amnestic disorders.
- In the hospital setting the incidence of alcohol-induced amnestic disorders is decreasing while that of amnestic disorders secondary to head trauma is on the rise
- Prevalence of alcohol-induced amnestic disorder: 0.2% to 4%
- Incidence of transient global ischemia: 5.2 cases per 100,000 per year.

Etiology

Seizure Disorders	Comments
Traumatic brain injury	The fastest growing cause of Amnestic disorder in the United States
Cerebral tumors	Mainly localized around the third ventricle
Stroke	In the posterior cerebral artery territory
Paraneoplastic syndromes (limbic encephalitis)	Focal inflammation of the temporal lobes
Infections (herpes simplex encephalitis)	Preferentially attacks the temporal lobes and produces a hemorrhagic necrosis

Etiology

Seizure Disorders	Comments
Metabolic (hypoxia)	Several causes (respiratory, cardiovascular, metabolic compromise or carbon monoxide intoxication) attacking the sensitive CA1 hippocampal region
Transient global amnesia	Profound anterograde and retrograde amnesia improving over the course of several days
ECT	Retrograde amnesia that usually remits after days/weeks

Etiology

Systemic conditions

- Alcohol-induced amnestic syndrome (Korsakoff's syndrome)
- Thiamine deficiency
- Hypoglycemia
- Substance-induced amnestic disorder (excluding alcohol) sedative-hypnotics

Symptoms and Types

- Anterograde amnesia - inability to learn new information
- Retrograde amnesia - inability to recall previously learned information
- Memory for the event that produced the deficit (e.g., a head injury in a motor vehicle accident) may also be impaired.
- Immediate recall is usually not affected.
- Short-term memory can also be impaired to a variable degree.
- Long-term retrograde memory impairment is temporally graded (more remote memories are better preserved).

Symptoms and Types

- Attention and implicit learning remains intact.
- Associated symptoms include
  - Confabulations - more frequent in diencephalic amnesia (Korsakoff's syndrome) than in hippocampal amnesia.
  - Changes in personality (apathy, lack of initiative, impulsivity)
  - Neurological symptoms corresponding to the underlying illness (stroke/multiple sclerosis/alcohol-induced amnestic syndrome).

Areas of the Brain involved

- Mamillary bodies, hippocampus, amygdala, dorsomedial and midline thalamic nuclei.
- Bilateral lesions - most common cause, but some studies show unilateral (L>R) damage as the cause of amnestic disorders.
- Frontal lobe involvement - may be responsible for symptoms like apathy and confabulation.

Medial Temporal Lobe & Diencephalic Amnesia

Medial Temporal Lobe Amnesia

- Short term memory is normal
- Severe anterograde memory loss
- Once learned there is rapid rate of forgetting.
- Retrograde memory loss is temporarily graded, but limited
- Semantic memory is preserved
- Normal implicit memory

Diencephalic Amnesia

- Short term memory is normal
- Severe anterograde memory loss
- Once learned there is rapid rate of forgetting.
- Retrograde memory loss is temporarily graded, but extensive
- Semantic memory is preserved
- Normal implicit memory

Frontal Lobe Amnesia

- No real memory loss
- Due to poor attention & executive function
- Failure to recall, but normal recognition
- Certain specific impairments of memory:
    - Defective recall of temporal order
    - Defective recall of the context of the learned items
    - Defective judges of knowing what they remember

Diseases with Memory Loss

- Medial Temporal Lobe:
  - Encephalitis, Anoxia, PCA stroke
- Diencephalic:
  - Wernicke-Korsakoff's syndrome
  - Thalamic infarct
- Frontal Lobe:
  - Stroke or tumor affecting basal forebrain

Median Temporal Amnesia

- Herpes Simplex Encephalitis
  - Damage to medial & lateral temporal cortex.
  - Severe episodic memory loss
  - Semantic memory loss, if lateral temporal cortex is affected.
- Paraneoplastic Limbic Encephalitis
  - An autoimmune response to cancer
  - Similar to HSE
- Anoxic Encephalopathy
  - Causes: cardiac arrest, respiratory distress, strangulation or CO poisoning.
  - Susceptible areas: Hippocampus, Cerebellum, Basal ganglia
  - Most vulnerable: CA1 segment
  - Mild to severe memory loss.

Median Temporal Amnesia

- Strokes
  - PC infarction
    - Supply post. Hippocampus, parahippocampal gyrus & connections of hippocampus
    - Bilateral lesion: Global amnesia
    - Unilateral stroke: Material specific memory loss
  - Thalamic strokes
    - Affecting mamillothalamic tract & internal medullary lamina

Wernicke's Encephalopathy

Causes

- Thiamine deficiency
  - Chronic alcoholism
  - Ca stomach
  - Toxemia of pregnancy
  - Vomiting
  - Diarrhoea
  - Pernicious anaemia
  - Dietary deficiency
- Association b/w alcoholism & Wernicke's encephalopathy explained by certain mechanisms.

Wernicke's Encephalopathy

Clinical Features:

- Acute onset
- Global Confusion– 90%
- Ocular abnormalities – 96%
- Ataxia
- Memory disturbances quite prominent when confusion subsides
- Peripheral neuropathy, malnutrition, frank DT.

Wernicke's Encephalopathy

Investigations:

- Raised blood pyruvate level (non specific)
- Red cell Transketolase estimation

Pathology:

- Changes in 3rd ventricle, peri-aqueductal region, dorsomedial nuclei of pulvinar, mamillary bodies, anterior lobe of cerebellum
- Cerebral cortex affected in 27%.

Wernicke’s Encephalopathy

Treatment:

- Correct Thiamine deficiency by 50mg thiamine IV followed by IM injection of 100mg thiamine daily till improvement
- Magnesium supplementation
- Correct other nutritional & vitamin deficiencies

Korsakoff's Syndrome

History

- 1869 – Carl Wernicke described acute encephalopathy caused by chronic alcohol use (Wernicke's Encephalopathy)
- 1889 - Serghei Korsakoff described a syndrome of polyneuritis, anterograde amnesia, and confabulations in subjects with chronic alcohol use; did not differentiate it from Wernicke's encephalopathy
- 20th century – Karl Boenhoffer gave the connection between Wernick's encepahlopathy and Korsakoff's psychosis

Korsakoff’s Syndrome - History

- Emil Kraepelin - distinguished between alcohol-related Korsakoff's syndrome and Korsakoff's syndrome caused by other nonalcoholic processes (neurosyphilis).
- Early 1930s – Correlation between Korsakoff's syndrome and thiamine deficiency caused by poor nutrition associated with chronic alcohol use
- 1960s - Maurice Victor described the corresponding diencephalic lesion

Wernicke-Korsakoff’s Syndrome

- Korsakoff's syndrome usually develops secondary to Wernicke's encephalopathy, and frequently they are described together (Wernicke-Korsakoff's syndrome)
- Some cases of Korsakoff's syndrome develop in the absence of the initial stage of acute Wernicke encephalopathy.
- Korsakoff's psychosis, Korsakoff's dementia, and Korsakoff's syndrome have been used interchangeably to describe the clinical presentation of alcohol-induced amnestic disorder.

Incidence

- Incidence of Wernicke's encephalopathy and Korsakoff's syndrome are ~ 0.4% in France and ~ 2% in the United States, Scandinavia, and Australia.
- Seen in subjects over age 40 (duration of alcohol use >20 yrs).

Role of Thiamine

- Thiamine pyrophosphate (TPP) - active form of thiamine - involved in three enzymatic reactions important for the metabolism of glucose and the production of several neurotransmitters
- Thiamine deficiency causes selective loss of neurons for which various mechanisms have been proposed.

Causes of Thiamine Deficiency

- Alcohol
  - Folate deficiency, which reduces the absorption of thiamine from the GI tract
  - Direct damage to the intestinal mucosa
- Primary thiamine deficiency
  - General malnutrition
  - Anorexia nervosa
  - AIDS
  - Hyperemesis gravidarum
  - Thyrotoxicosis
  - Metastatic cancer
  - Hypomagnesemia
  - Long-term dialysis
  - CHF treated with diuretics

Mechanisms

- Breakdown of the blood–brain barrier
- Altered glutamate neurotransmission caused by extracellular glutamate and its impaired transport function, together with NMDA receptor-mediated excitotoxicity
- Accumulation of amyloid precusor-like protein
- Increased free radical production
- Increased expression of superoxide dismutase in response to increased microglial response
- Induction of nitric oxide
- Oxidative stress.

Mechanisms

- Acetylcholine, GABA, glutamate, and aspartate are produced by oxidative metabolism of glucose.
- Serotonin metabolism - influenced by thiamine deficiency. CSF levels of 5-HIAA were decreased in patients with Wernicke-Korsakoff's syndrome; Thiamine may inhibit serotonin uptake; deficiency may be associated with behavioral and mood changes.
- Anatomical lesions in the medial dorsal thalamic nuclei, the mammilary bodies, the fornix, and the cerebellum.
- Lesions in anterior thalamic nuclei, mamillary complex are related to impaired explicit memory.

Features

- Patients with Korsakoff's syndrome, while maintaining an overall intact intelligence, are unable to form new memories (anterograde amnesia).
- Retrograde amnesia - less severe, although present to a certain degree (usually for events that occurred shortly before the onset of the illness).
- Immediate recall and implicit learning (e.g., learning procedures) are preserved.
- Confabulation present - an attempt to cover the memory deficit.

Transient Amnesic Syndromes

- TGA
- Migraine
- Transient epileptic amnesia
- IV contrast infusion
- TIA of posterior circulation
- SAH
- Head trauma

Transient Global Amnesia

- Described by Fisher and Adams
- D/D of Amnestic Syndrome
- Memory deficit - most characteristic feature
- Late middle/old age
- Male > Female
- Abrupt & sudden onset
- Episodic attacks: hours–few days

Transient Global Amnesia

- Complete recovery
- Retrograde amnesia recovers before anterograde amnesia
- Impairment of all aspects of memory, state of puzzled bewilderment
- Preceded by headache, vigorous exercise, stress, medical procedure
- Patient can attend personal needs, aware of personal identity
- Recurrence rare
- Sometimes permanent deficit in the form of memory impairment & global cognitive impairment.

Transient Epileptic Amnesia

- Coined by Kapur
- Refers to pts with TGA with epilepsy
- Recurrent brief (< 1hr) amnesic episodes
- Often occur upon waking
- May be associated with olfactory hallucinations or automatisms
- EEG & CT may be normal
- Sleep EEG recordings may be helpful
- Involvement of B/L limbic structures as well as the mesial diencephalon

Head Injury

- Some retrograde amnesia
- PTA may exist without retrograde amnesia, although this is more common with penetrating lesions
- Length of PTA predictive of eventual cognitive/psychiatric/social outcome
- PTA needs to be distinguished from the post traumatic syndrome

Alcoholic Blackouts

- Periods of amnesia for events occurring during heavy drinking
- Related to the BAC
- Common in binge drinkers
- ‘Fragmentary’ blackouts
- ‘En bloc’ blackouts
- Hypoglycemia may be contributory
- H/o head injuries

Iatrogenic Amnesia

ECT

- Retrograde memory impairment from the preceding 1-3 years
- A pronounced anterograde memory impairment on recall & recognition tasks
- Accelerated rate of forgetting
- Returns to normal within 6-9 months
- Verbal memory is particularly sensitive to disruption

Iatrogenic Amnesia

Drugs

- BZD- especially triazolam
- Barbiturates (thiopental sodium)
- Diltiazem
- Zalcitabine
- Flunitrazepam

Assessment

- Neuropsychological testing - discrepancy b/w performances on memory scales and general cognitive scale
- Laboratory tests - evidence of chronic alcohol use, malnutrition, vitamin deficiency, or systemic illness.
- Neuroimaging tests - to differentiate between several causes of amnestic syndrome

Neuropsychological Testing

- Patient has to be alert, attentive & cooperative
- Short term memory
  - Digit span.
- Long term memory
  - Multiple trial list learning task.
  - Recognition- by mixing items from the learned list with similar items not in the list
- Remote memory
  - Naming or describing remote personal or historical events
- Semantic memory
  - Ask questions about commonly known facts

Laboratory Tests

Include blood and urine to test for

- Infections
- Renal and liver function tests
- Hypoglycemia and diabetes
- Electrolyte imbalances
- Metabolic and endocrine disorders
- Nutritional deficiencies, B12, folate
- Presence of toxic substances

Neuroimaging Tests

CT/MRI

- Mammillary bodies atrophy in Korsakoff's syndrome,
- Strategic localized strokes,
- Anoxic lesions of the hippocampal structures,
- T2-weighted hyperintensities in bilateral temporal poles in herpes encephalitis

Differential

- Amnestic disorders v/s Delirium:
  - Amnestic disorders - clear consciousness and intact attention, with no perceptual disturbances or mood lability; no impairment in abstract thinking, judgment, or executive functions.
  - Cognitive impairment in dementia extends to semantic memory, language, and praxis.
- Psychogenic amnesia:
  - Presentation - onset after traumatic event; no evidence of substance/general medical condition; amnesia for personal identity conserved in amnestic disorder, and for a circumscribed event, but preserved memory for new events and preserved ability for learning)
  - Course - abrupt onset and resolution, no residual impairment

Course and Prognosis

- Around 25% of patients with Korsakoff's syndrome recover
- Rest continue to suffer from various degrees of memory impairment, a significant minority needing permanent placement.
- Most amnestic syndromes have a stable course.
- A few would recover (TGA, post ECT amnesia) or improve (amnestic disorder following traumatic brain injury)

Treatment

- Wernickes’s encephalopathy: High dose Thiamine (1-2g daily)
- Korsakoff’s syndrome: Donepezil, Memantine and Rivastigmine
- Treatment of underlying cause, if any
  - Acyclovir - herpes encephalitis
  - Hyperbaric oxygen - carbon monoxide poisoning
- Cognitive rehabilitation programs - improve the patient's level of functioning, but are of dubious efficacy regarding restoring/improving memory in the impaired domain.

Treatment

- Psychoeducate the family members
- **Suggest planning** care for patient
- **Understanding &** a**ccept**
- **Environmental** m**anipulation**
- **Supportive** g**roup for** family members
- **Individual** psychotherapy f**or** family m**ember**s

Summary

- Diagnostic entities included in DSM-IV-TR, DSM-5 and ICD-10 definition
- Structures that are involved
- Etiology: Head injury & alcohol abuse are common causes
- Wernicke-Koraskoff syndrome
- Differential diagnosis
- Treat the cause
- Family psychoeducation

References

- Benjamin J. Sadock, Virginia A. Sadock, Pedro Ruiz Kaplan and Sadocks Comprehensive Textbook of Psychaitry
- New Oxford Textbook of Psychiatry - Michael G. Gelder
- Internet

Thank You