Spectrum of Limbic Involvement in Toxic Ingestion:
Two Cases of Anterograde Amnesia

Dylan Lahiff, MD[1,3], Colin Harrington, MD, DFAPA, FACLP, FANPA[1], Kimberley R. Chapman[1], PhD, Seth Margolis[1], PhD
[1]Brown University, Providence, RI
[2]USF Morsani College of Medicine, Tampa, FL

BROWN
Alpert Medical School

Papez Loop (Medial Limbic Circuit)

- Originally theorized as basis for emotional experience
- Now thought to mediate the formation of new memories
- Composed of: hippocampus, fornix, mamillary body, anterior thalamic nuclei, cingulate gyrus, parahippocampal gyrus
- Damage to any part of this circuit can lead to varying degrees of anterograde and retrograde amnesia – phenotype similar to Korsakoff Syndrome

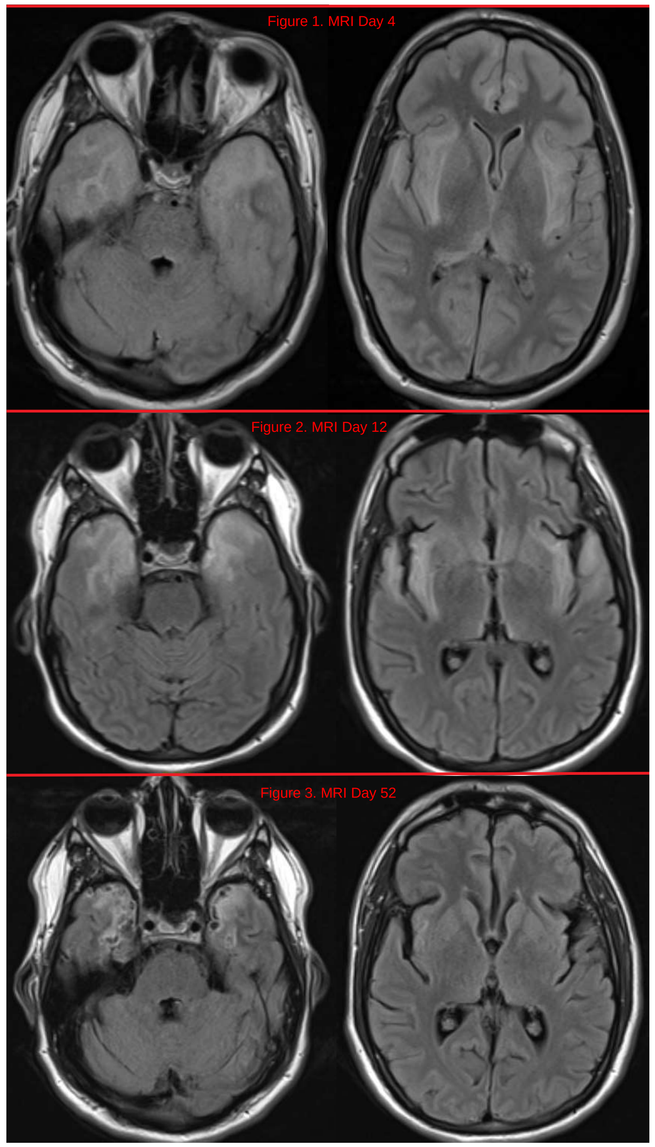
Opiate Associated Amnestic Syndrome (OAAS)

- Sudden onset amnesia following ingestion of opiates
- Bilateral hippocampal diffusion restriction seen on MRI. Longitudinal imaging shows resolution of MRI changes in some cases[1]
- Hippocampus susceptible to toxic/hypoxic injury due to high degree of vascularization
- Degree of reversibility varies. Predictive factors for recovery are lacking due to paucity of case reports literature
- Significant hippocampal volume loss seen in patients with opiate use disorder with history of overdose vs. patients without overdose[3]
- Similar cases have been described following benzodiazepine and cocaine use

Patient A

- 53-year-old woman who was found down in her home, with possible seizure activity witnessed by EMS
- Medical History: Unremarkable
- Psychiatric History:
    - Dx: Opioid Use Disorder
    - Multiple admissions for overdose with clinical improvement following Narcan administration
- Toxicology positive for fentanyl only
- Toxic-metabolic workup unremarkable
- EEG notable for epileptiform activity. AEDs initiated
- Anterograde amnesia and loss of autobiographical information persisted after clearing of delirium
- MRI demonstrated severe diffusion restriction in bilateral hippocampi which persisted at HD 28. Long term reversibility of amnesia remains uncertain, awaiting continued follow-up.

MRI Brain Progression – Patient B



Impression Across 3 MRIs:

Initial edema in bilateral temporal poles (hippocampus), amygdala, parahippocampal gyri, cingulate gyri and anterior nuclei of thalamus.

Final read (MRI #3) with persistent severe, symmetric microcystic encephalomalacia of the bilateral temporal neocortex (temporal poles and inferior temporal neocortex), amygdala, hippocampal head and anterior cingulate cortex.

Patient B

- 34-year-old male brought in by EMS after being found down in parking lot with diarrhea, appearing confused and agitated
- Medical History: Unremarkable
- Psychiatric History:
    - Dx- ADHD, Generalized Anxiety Disorder, Autism Spectrum Disorder, Polysubstance Abuse
    - Multiple presentations with polysubstance use (Dextromethorphan, alcohol, GHB, benzodiazepines, prescribed stimulants), occasionally with associated psychosis
    - Chronic suicidal ideation
- Recent 7-day admission for accidental overdose on dextromethorphan with psychosis. Presented on the evening of day of discharge
- Toxic metabolic workup significant for sodium 178, chloride 149, lactate 5.4, urine osmolarity 611, urine sodium 256, UDS with cannabinoids only, Hgb 17.7 and WBCs 20. Fever to 101.5F
- Required intubation for airway protection. Admitted to MICU
- Sodium corrected from peak of 180 to 148 over 70 hours
- Comprehensive tox screen positive for dextromethorphan, methylphenidate and derivatives
- Initial MRI Brain Day 4 for persistent confusion (see figure 1, left) – **notable for involvement of 4 elements of Papez Loop**
- Further workup including LP, EEG and cultures unremarkable
- Initially delirious on exam, rapidly improved with notable exception of continued deficits in memory
- Second MRI Brain Day 12 (see figure 2, left) due to memory deficits
- Cognitive exam essentially unchanged for remainder of admission, moderate retrograde amnesia and profound anterograde amnesia
- Final MRI Brain Day 52 (see figure 3, left)

Possible Mechanisms

- Role of sodium correction considered. Drop in sodium within recommended rate of <0.5mEq/L/hr. Literature does not support changes similar to rapid correction of hyponatremia
- Possible restriction of blood flow to areas of brain affected by edema, as proposed in OAAS
- Dextromethorphan toxicity: Animal model studies with dextromethorphan note neurotoxic effect at high concentrations, damage to bilateral hippocampi by myeloid body formation[3,4]
- Diffusion restriction on MRI seen in patient B may represent expanded pattern of bilateral damage seen with OAAS

References: 1. Baresh et al. 2023, PMID: 37389894, 2. Todaro et al. 2023, PMID: 37753562, 3. Tortella et al. 1999, PMID: 10490930, 4. Tran et al. 2016, PMID: 27802908