Diagnostic approach to the HIV infected patient with altered mental state

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Plan

- Definitions
- Pathogenesis
- Risk factors
- History
- Examination
- Investigations
- Algorithms
Definitions

Confusion: inability to maintain a coherent stream of thought or action
Requirements for normal neuronal activity

- Balanced environment
- Electrolytes
- Water
- Amino acids
- Excitatory and inhibitory neurotransmitters
- Metabolic substrates
- Normal blood flow, pH, osmolality, temperature
<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden, abrupt</td>
<td>Insidious, slow</td>
</tr>
<tr>
<td><strong>Course over 24 hours</strong></td>
<td>Fluctuating</td>
<td>Usually stable</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Hours - weeks</td>
<td>Months - years</td>
</tr>
<tr>
<td><strong>Consciousness</strong></td>
<td>Reduced</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>Alertness</strong></td>
<td>Variable, or variable</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Psychomotor activity</strong></td>
<td>Variable, or mixed</td>
<td>Normal, may have apraxias</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Globally disordered</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Usually impaired</td>
<td>Often impaired</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>Incoherent</td>
<td>Difficulty with word finding</td>
</tr>
<tr>
<td><strong>Affect</strong></td>
<td>Variable</td>
<td>Labile</td>
</tr>
<tr>
<td><strong>Disturbed perceptions</strong></td>
<td>Illusions and visual hallucinations, Delusions, fleeting and often percutory</td>
<td>Late</td>
</tr>
<tr>
<td><strong>Affect and mood</strong></td>
<td>Apathy, anxiety, fear and terror</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Disturbance in sleep wake cycle</strong></td>
<td>Early</td>
<td></td>
</tr>
</tbody>
</table>
Key Features Of Delirium

- Altered level of consciousness, ranging from stupor to agitation
- Inattention, decreased ability to focus
- Fluctuating course over hours or days
- Disturbance in sleep/wake cycle
- Precipitated by medical illness, substance intoxication/withdrawal, or medication effect
Factors Contributing to Changes in Neurotransmitters, Leading to Delirium

↓ACH = Neuronal Excitability
- Anticholinergic drugs
- Age/dementia
- Hypoxia
- Anemia
- Hypotension
- Poor nutrition
- Infection
- Surgery
- Alzheimer’s disease

↑DA = ↓Release of ACH
- Drugs: dopamine agonists
- Infection
- Surgery
- Age/dementia

Mechanisms of Delirium Neurotransmitters

↑Cortisol & Beta-Endorphins
- Exogenous glucocorticoids
- Disruption of circadian rhythm

↓GABA = Neuronal Excitability
- Benzodiazepines
- Alcohol withdrawal

↑Serotonin
- Antidepressants
- Infection
- Hepatic encephalopathy

ACH: acetylcholine; DA: dopamine; GABA: gamma-aminobutyric acid.
Source: References 1, 7-11.
Prostaglandins and cytokines from circumventricular organs are involved in the brain. Afferent signals from the periphery (e.g., vagus nerve) and pathogen-associated molecular patterns influence endothelial cells and perivascular macrophages at the blood-brain barrier.
Periphery: acute insult

- Infection
- Injury
- Surgery (etc.)

- Tissue macrophages

- IL-1β
- TNF-α
- IL-6
- IFN-α/β
- PGE2

- Activation of LHPA axis, e.g. via CRH in hypothalamus

- Endothelial cells of cerebral vasculature

- GCs

Vulnerable brain: ageing / dementia

- Primed microglia

- IL-1β
- TNF-α
- PGE2

- Mediators

- GCs
- PGE2

- Damaged neurons

- Acutely impaired neuronal function

- Delirium

Adrenal cortex
Incident factors:
Toxic
Metabolic
Brain lesion

Predisposing factors:
Age
Dementia

Delirium
## RISK FACTORS OF DELIRIUM

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>Precipitating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt; 65)</td>
<td>Polypharmacy</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Infection</td>
</tr>
<tr>
<td>Physical frailty</td>
<td>Immobility</td>
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<tr>
<td>Visual impairment</td>
<td>Catheters</td>
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<tr>
<td>Hearing impairment</td>
<td>Sleep deprivation</td>
</tr>
<tr>
<td>Male sex</td>
<td>Use of restraints (physical and pharmacological)</td>
</tr>
<tr>
<td>Dehydration on admission</td>
<td>Pain</td>
</tr>
<tr>
<td>Infection on admission</td>
<td>High number of hospital procedures</td>
</tr>
<tr>
<td>Multiple comorbidities</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Electrolyte disturbance</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>End organ failure</td>
</tr>
<tr>
<td>Previous episodes of delirium</td>
<td>Alcohol withdrawal</td>
</tr>
</tbody>
</table>
Schematic representation of the main pathophysiological mechanisms of SAE. The inflammatory response is represented by TNF-α induction, which increases BBB damage and the liberation of aquaporin 4 to cause brain edema. Mitochondrial dysfunction and the reduction in oxidative phosphorylation efficiency (cytochrome c malfunction) may induce apoptosis and trigger brain injury. The accumulation of false neurotransmitters may increase intracellular calcium content and contribute to encephalopathy. Cerebral perfusion may be altered, rendering brain function more susceptible to injury. TNF-α: Tumor necrosis factor α. NO: nitric oxide. LNAA: Large, neutral amino acids. BCAA: Branched-chain amino acids. SAE: sepsis-associated encephalopathy. BBB: blood-brain barrier.
Inflammatory markers and studies that show their link to delirium and dementia

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pro/anti-inflammatory</th>
<th>Role in delirium and dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1</strong></td>
<td>Proinflammatory</td>
<td>Increases neuronal tau phosphorylation and activates astrocytes; polymorphism linked to increased risk of AD; levels elevated in AD</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>Proinflammatory</td>
<td>Levels elevated in delirium; polymorphism linked to increased risk of AD; levels linked to gray matter volume and memory function; levels elevated in non-AD dementia</td>
</tr>
<tr>
<td><strong>IL-8</strong></td>
<td>Proinflammatory</td>
<td>Levels elevated in delirium</td>
</tr>
<tr>
<td><strong>IL-RA</strong></td>
<td>Anti-inflammatory</td>
<td>Levels decreased in delirium</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td>Proinflammatory</td>
<td>Polymorphism linked to increased risk of AD; levels elevated in AD; elevated levels linked to cognitive decline</td>
</tr>
<tr>
<td><strong>IGF-1</strong></td>
<td>Anti-inflammatory</td>
<td>Levels decreased in delirium</td>
</tr>
<tr>
<td><strong>IFN-γ</strong></td>
<td>Proinflammatory</td>
<td>Levels decreased in delirium</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>Proinflammatory</td>
<td>Higher levels linked to poor cognitive performance/increased risk of cognitive decline</td>
</tr>
</tbody>
</table>
History

- The Patient
- The wife/partner
- The relative
- The friend
- The neighbour
- The work mate
Mental State Examination

- Impaired attention
- Decreased alertness
- Hallucinations
- Impaired memory
- Disorientation
- Apathetic, withdrawn
- Anxious, agitated, fearful

LOC reflects severity of underlying condition

- Seductive (try anything once!)
- Evasive (it's called privacy)
- Unshaven (no razor)
- Body odour (homeless)
- Halitosis (no teeth left)
- Dishevelled (try poverty)
- Inappropriate (self-empowering)
- Psychomotor agitation (side effects?)
- Grieving (surprise, surprise)
- Bad dreaming (of being imprisoned)
- Angry (at being interrogated)
- Shuffle (blistered, shop shoes)

- Delusions of grandeur
- Impaired insight
- Automatic judgement
- Word salad (jargon)
- Localised amnesia
- Recent memory deficit
- Often distracted
- Irrelevant answers
- Incoherence
- History of violence
- Persecutory delusions
- Thought broadcasting
- Time disorientation

- March
- Militaristic

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Physical examination

- Complete
- General
- All systems
- Pupils
- Hemiparesis/plegia
- Fundi
- Urine dipstix
Neck stiffness
Choroidal tuberculosis

Miliary choroids (tubercles) appear as ill-defined nodules varying in size from pinpoint to several disc diameters on funduscopic
Disseminated cryptococcosis

Multiple umbilicated papules are present on the face of this patient with cryptococcosis. The lesions resemble molluscum contagiosum.
Investigations

- Glucose
- Urea and electrolytes, Ca, Phos, Mag, LFTs
- Serum osmolality
- ABG
- Toxicology screen
- CSF examination
- TFTs, Vit B12, serum cortisol
- EEG, ECG
Midsagittal section through lumbar spinal column showing positioning for measurement of CSF opening pressure. The manometer is attached to the spinal needle hub with a three-way stop-cock. CSF is permitted to enter the manometer; opening pressure is recorded at the highest level attained by the CSF in the manometer column. Pressure measurements should be taken with the patient recumbent.
Cryptococcus neoformans in cerebrospinal fluid

Gram stain of cerebrospinal fluid (x1000) shows likely yeast forms, a few with cell walls and budding. These forms can be confused with host cells on the Gram stain and are more easily identified by India ink. The most definitive procedures are testing for cryptococcal antigen and culture. Cryptococcus neoformans grew from this specimen.
Cryptococcus neoformans in an India ink preparation

India ink preparation of cerebrospinal fluid (x400) shows a prominent clear zone around individual yeasts, consistent with the capsule of Cryptococcus neoformans. The yeast in the center of the slide is budding.
EEG in dementia and encephalopathy
Imaging

- CXR
- CT brain
- MRI brain
Central nervous system lesions

- Degree of immune suppression
  - CD4 > 500: TB meningitis, brain tumours, metastases
  - CD4 200-500: TBM, HIV associated motor and cognitive disorders
  - CD4 <200: Cryptococcus, TBM, Toxoplasma encephalitis, CMV encephalitis, herpes encephalitis, HIV encephalopathy, Primary CNS lymphoma, PML,
Useful radiological features

- MRI
- More sensitive
- Determining whether a lesion is truly solitary
- White matter disease
- Posterior fossa lesions
- Biopsy procedure: choice of lesion
Lesions with mass effect

- Toxoplasmosis
- TB
- Primary CNS lymphoma
Toxoplasma encephalitis

- Toxoplasma antibodies
- Multiple lesions
- Parietal or frontal lobes
- Thalamus, basal ganglia
- Cortico- medullary junction
- Ring enhancement and surrounding oedema in 90% cases
- Uncommonly: diffuse encephalitis with no abscesses
Multiple ring enhancing lesions with mass effect are visible after injection of gadolinium in this T1-weighted image.
Primary CNS lymphoma

- Solitary and multiple lesions occur with equal frequency
- Irregular, patchy enhancement
- Corpus callosum, periventricular
- Lesions > 4cm more likely PCNC lymphoma
A nodular enhancing lesion produces moderate mass effect on the frontal horn of the right lateral ventricle in this T1-weighted image.
Other infections with mass effect

- Tuberculomas
- Brain abscesses: crypto, syphillis, neurocysticercosis, staph, strep, aspergillus, nocardia,
CNC lesions without mass effect

- Progressive multifocal leukoencephalopathy
- JC virus
- Demyelination
- Multifocal areas, bilateral, asymmetrical
- Periventricular areas, subcortical matter
- Not contrast enhancing
- No surrounding oedema
- Exception: IRIS
AIDS patient with progressive multifocal leukoencephalopathy (PML)

There is a focal area of low density on CT scan (A) which involves the right periventricular white matter and extends peripherally to involve the subcortical white matter. MRI of same patient shows the lesion to be hyperintense on T2-weighted (B) and FLAIR (C) images, without contrast enhancement on post-contrast T1-weighted image (D). Diffusion-weighted image (E) shows increased signal intensity with a more hyperintense ring along the periphery, or advancing edge of the lesion. MR Spectroscopy of this lesion (F) shows that this lesion has characteristic decreased NAA, increased MI, increased choline, and elevated lactate/lipid peaks. (see Izano et al).

mI: myo-inositol; Ch: choline; Cr: creatine; NAA: N-acetyl-aspartate; Lac/Lip: lactate/lipids.
HIV encephalopathy

- Classic triad
- Memory and psychomotor speed impairment
- Depression
- Movement disorders
- Multiple non enhancing lesions
- Bilateral
- Subcortical
- Symmetrical, less well demarcated
MRI of the brain from a patient with HIV-associated dementia

Bilateral symmetrical high T2 signals without mass effect are present in the white matter of both frontal lobes, associated with subcortical atrophy.
CMV encephalitis

- CD4 < 50
- Micronodular encephalitis or ventriculoencephalitis
- Cortex, basal ganglia, brain stem, cerebellum,
- Rarely ring enhancing mass lesions with oedema
Ancillary imaging studies

- Thallium 201 SPECT: lymphoma vs toxo
- Perfusion MRI: Toxo vs PCNSL
- MR spectroscopy
- Positron emission tomography (PET): Toxo vs PCNSL
CSF

- TBM, Cryptococcus, bacterial meningitis
- In mass lesions, utility limited
- Pleocytosis, elevated protein non specific
- CNS lymphoma: cytology diagnostic in 15 %
CSF PCR

- DNA of JC virus, Toxo, EB virus
- JC virus: sensitivity 74-93%, specificity 92-100%
- EBV DNA less clear
- Toxo: sensitivity 50%; specificity 96-100%
- CMV encephalitis: sensitivity > 80%; specificity > 90%
- Herpes simplex encephalitis
MRI findings in a patient with herpes simplex encephalitis

(Upper panels) Magnetic resonance (MR) images of the brain of a patient with herpes simplex virus encephalitis at two day after admission. Abnormal signals were seen in the right temporal lobe and insular cortex.
(Lower panels) MR images showing that abnormal signals had spread to the left side at 15 days after admission.
Stereotactic brain biopsy

- Gold standard for diagnosis of mass lesions
- Mortality 0-3.1%
- Major morbidity: 0.5-9%
- Minor morbidity: 2-4%
- Definitive diagnosis reached in 93-96%
Assessment and management of patient with delirium

Patient with delirium (DSM-IV or CAM diagnosis)

Institute supportive measures:
- Maintain hydration
- Avoid restraints
- Mobilize patient
- Reduce noise
- Orienting stimuli (e.g., windows)
- Reassurance
- Bedside sitters

Does patient behavior interfere with care or safety?
- Yes
  - Low dose neuroleptic (haloperidol, risperidone, etc) and/or low dose, short acting benzodiazepine
  - Continue evaluation and treatment

- No

Review medications; perform focused history, physical; obtain basic lab studies (CBC, glucose electrolytes, creatinine, BUN, calcium, urinalysis, pulse oximetry, EKG)

Offending drug?
- Yes
  - Discontinue
- No

Trauma or focal finding?
- Yes
  - CT scan of brain
- No

Focus of infection?
- Yes
  - Begin antibiotic therapy
- No

Unexplained fever/nuchal rigidity?
- Yes
  - Perform lumbar puncture
- No

No obvious etiology?
- Yes
  - Consider:
    - B12/folate
    - Thyroid tests
    - EEG
    - MRI
    - Drug levels
    - Toxin screen

Patient improves?
- Yes
  - Patient discharged to appropriate postacute setting
- No
  - Reassess patient; consider prolonged delirium syndrome

Predisposing causes for delirium

Patient characteristics:
- age
- alcohol
- gender
- living single at home
- smoking

Environment:
- admission via emergency room
- admission via transfer
- isolation
- no clock
- no visible daylight
- no visit
- open intensive care
- physical restraints

Limit or not modifiable:
- limited
- or not modifiable

Chronic pathology:
- predisposing cardiac disease
- predisposing cognitive impairment
- predisposing pulmonary disease

Acute illness:
- length of stay
- fever
- high risk of mortality
- internal medicine
- no normal food
- number of perfusions
- psychoactive medication
- sedation
- TISS 28
- tubes and catheters

More modifiable:
<table>
<thead>
<tr>
<th>Mnemonic for Reversible Causes of Delirium</th>
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</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Electrolyte disturbances</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Lack of drugs</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
</tr>
<tr>
<td><strong>Reduced sensory input</strong></td>
</tr>
<tr>
<td><strong>Intracranial</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Urinary, fecal</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Myocardial, pulmonary</strong></td>
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</tbody>
</table>
Algorithm for the management of HIV-infected patients with central nervous system mass lesions

HIV-infected patient with CNS symptoms
CD4 count/HIV viral load

CT/MRI

Lesion(s) with mass effect

Impending herniation

+ Steroids open biopsy decompression

Toxoplasma serology Prophylaxis for toxo SPECT

- Safe to LP

Anti toxo trial

CSF

Specific Rx

Clinical and radiologic improvement after 2 wks

- Continue Rx

+ Specific Rx

Biopsy

Safe to LP

- CSF*

+ Continue Rx

Elements in bold represent data which contribute to the decision-making process (see text for details).
Toxo: Toxoplasma encephalitis; LP: lumbar puncture; CSF: cerebrospinal fluid; Rx: treatment.