ACUTE CONFUSIONAL STATE WITH AND WITHOUT FEVER

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14th RTC Africa

Disclosures

I have no conflict of interest, whether or not related to the content of this presentation.

Confusional state

A decompensation of cerebral function in response to one or more pathophysiological stressors

European Delirium Association BMC Medicine, 2014

Most episodes lasting a few days but with episodes persisting for weeks or months in up to 20% of individuals

Jo Ellen Wilson, NATURE REVIEWS | DISEASE PRIMERS, 2020

Confusional state

Before DSM-III

- Acute confusional state
- Encephalopathy
- Acute brain failure
- ICU psychosis
- Subacute befuddlement

DSM-III (1980)

Delirium

European Delirium Association BMC Medicine, 2014

Terminology

Which term to use?

Delirium versus encephalopathy versus an acute confusional state

Expert consensus recommendation

- ***Acute encephalopathy*** → pathophysiologic state of the central nervous system "process,"
- ***Delirium*** → the symptoms observed at the bedside
- ***Acute confusional state, acute brain dysfunction, acute brain failure,*** **or** ***altered mental status*** → educational purposes

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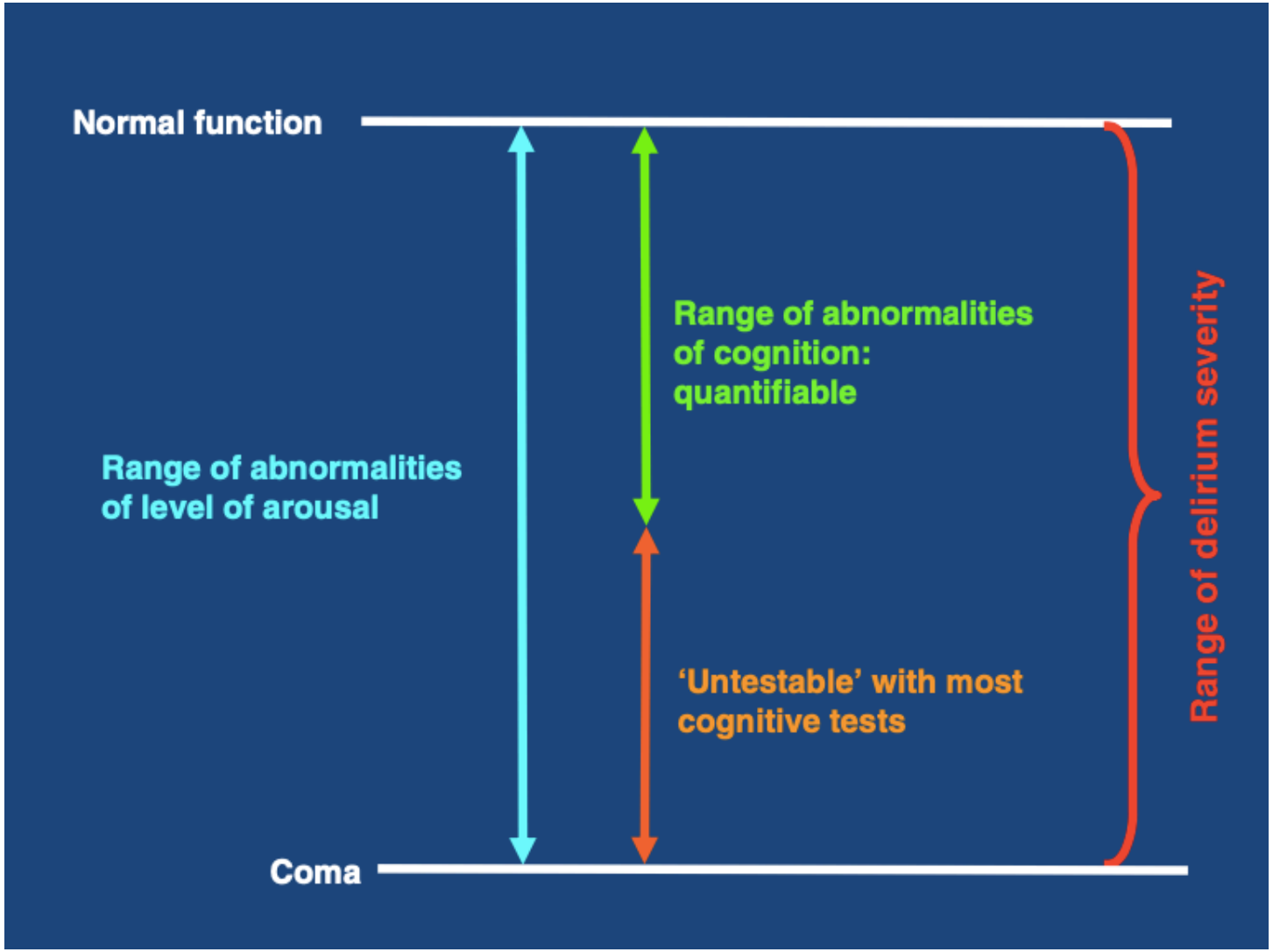
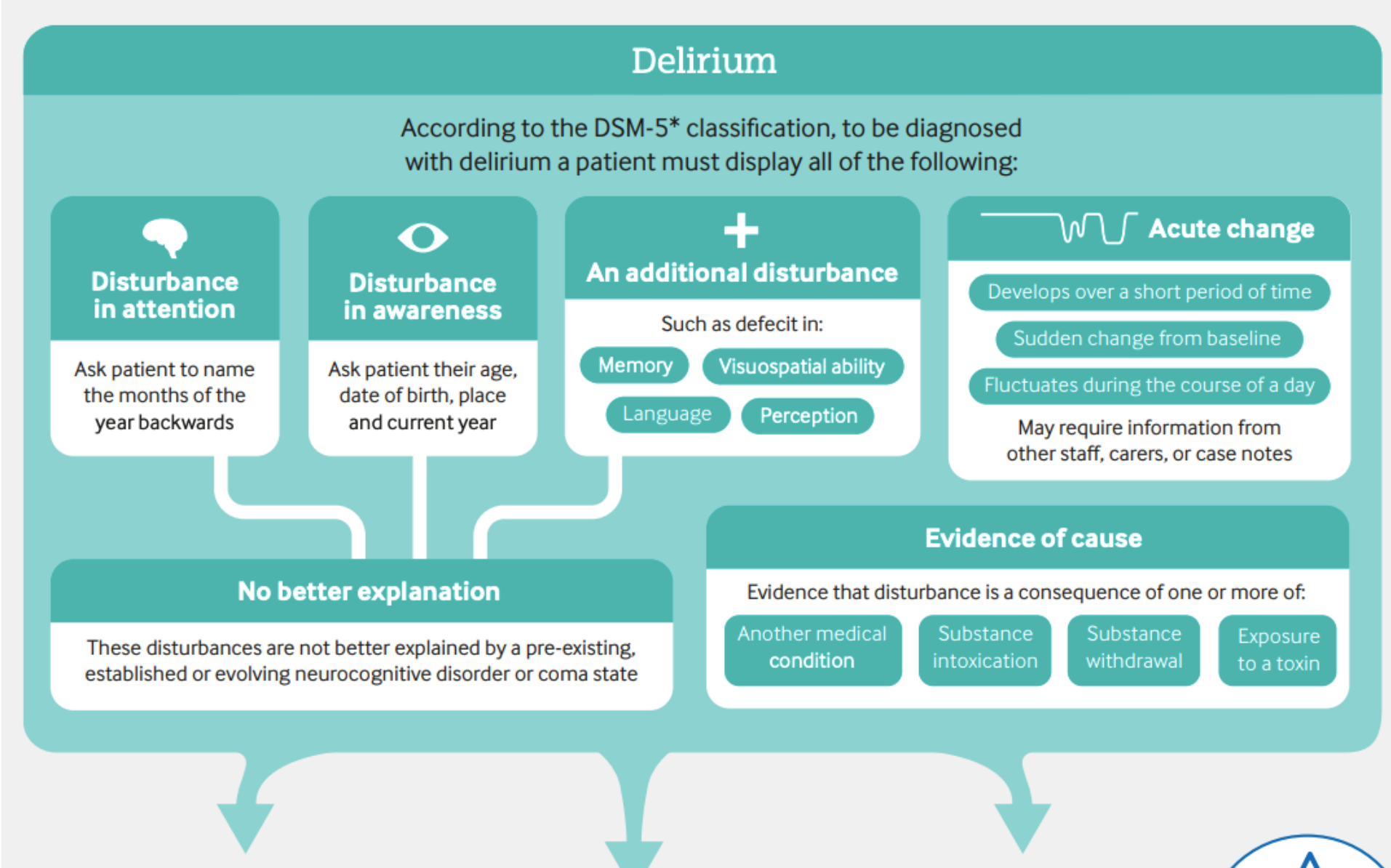
Confusional state

Overlap between hypoactive delirium and reduced arousal states *(hyperactive delirium not included)*



European Delirium Association BMC Medicine 2014

Diagnostic



Christian Hosker, David Ward, BMJ 2017

DSM Criteria evolution

Table 1 Comparing DSM classifications of delirium[a]

DSM-5	DSM-IV
A. Disturbance in *attention* (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*).	A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B. The disturbance develops over a short period of time (usually hours to a few days), *represents an acute change from baseline attention and awareness*, and tends to fluctuate in severity during the course of a day.	B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
C. An additional disturbance in cognition (e.g.memory deficit, disorientation, language, visuospatial ability, or perception).	C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma.*	D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.
E. There is evidence from the history, physical examination or laboratory findings that the disturbance is *a direct* physiological consequence of another medical condition, *substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.*	

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.
[a]Changes in DSM-5 from DSM-IV shown in *italics*.

Delirium subtypes

Hyperactive delirium

Predominantly restless and agitated

- Increased motor activity
- Loss of control of activity
- Restlessness
- Wandering

Mixed motor type

Evidence of both subtypes in the previous 24 hours

Hypoactive delirium

Commonly mistaken for depression or dementia

Predominantly drowsy and inactive

- Decreased activity
- Decreased action speed
- Decreased speed of speech
- Decreased amount of speech
- Reduced awareness of surroundings
- Listlessness
- Withdrawal

Christian Hosker, David Ward, BMJ 2017

DSM-V : Delirium

- **A. Disturbance in attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- **B.** The disturbance develops over a **short period of time (usually hours to a few days**), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
- **C. An additional disturbance in cognition** (e.g.memory deficit, disorientation, language, visuospatial ability, or perception).
- D. The disturbances in Criteria A and C are **not better explained by a pre-existing**, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.
- E. There is evidence from the history, physical examination or laboratory findings that the disturbance is **a direct physiological consequence** of **another medical condition**, **substance intoxication** or **withdrawal** (i.e. due to a drug of abuse or to a medication), or **exposure to a toxin**, or is due to **multiple etiologies**

When should clinicians consider a diagnosis of confusional state ?

- **Any confused hospitalized patient and in high-risk patients with confusion in any setting**

- **When in doubt : it is always better to rule out delirium first than to attribute confusion to an underlying chronic disorder, such as dementia, and fail to recognize delirium**

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Confusional state in practice

In the emergency room :

1. Diagnostic of confusional state	History – Examination
2. Rule out differential diagnoses	History – Examination
3. Search for the underlying cause	History – Examination +/- Clinical investigations

Diagnosis : History

History	
Time course of the mental status or behavioral changes	New onset, fluctuating course suggestive of delirium; usually obtained from family member or caregiver rather than patient; patient may also have symptoms of depression or dementia, but an acute change should prompt an evaluation for potential delirium
Association of mental status changes with other events, including medication changes and development of physical symptoms	Obtained from review of the medical record or from a family member or caregiver
Medication history, including over-the-counter medications	Careful review of all medications taken, including pharmacy fill data and information from electronic health record to ensure an accurate list of medications is obtained
Sensory deprivation assessment	Absence of glasses or hearing aids normally worn by the patient
Pain assessment	Delirium has been associated with severe pain, especially in patients unable to effectively communicate; pain may be manifested only by agitation

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Common risk factors

Predisposing conditions:

- Preexisting cognitive impairment
- Multiple comorbid conditions, including depression
- Polypharmacy
- Impaired sensation (e.g., vision, hearing)
- Impaired functional ability (i.e., activities of daily living diminished)
- History of alcohol misuse and/ or malnutrition
- Anemia

Precipitating factors:

- Severe illness (e.g., sepsis, stroke)
- Presence of tethers (e.g., urinary catheter) and/or physical restraints
- Surgery/anesthesia
- New psychoactive medication • Pain
- Environmental change
- Dehydration and/or electrolyte disturbances
- Urine retention/fecal impaction

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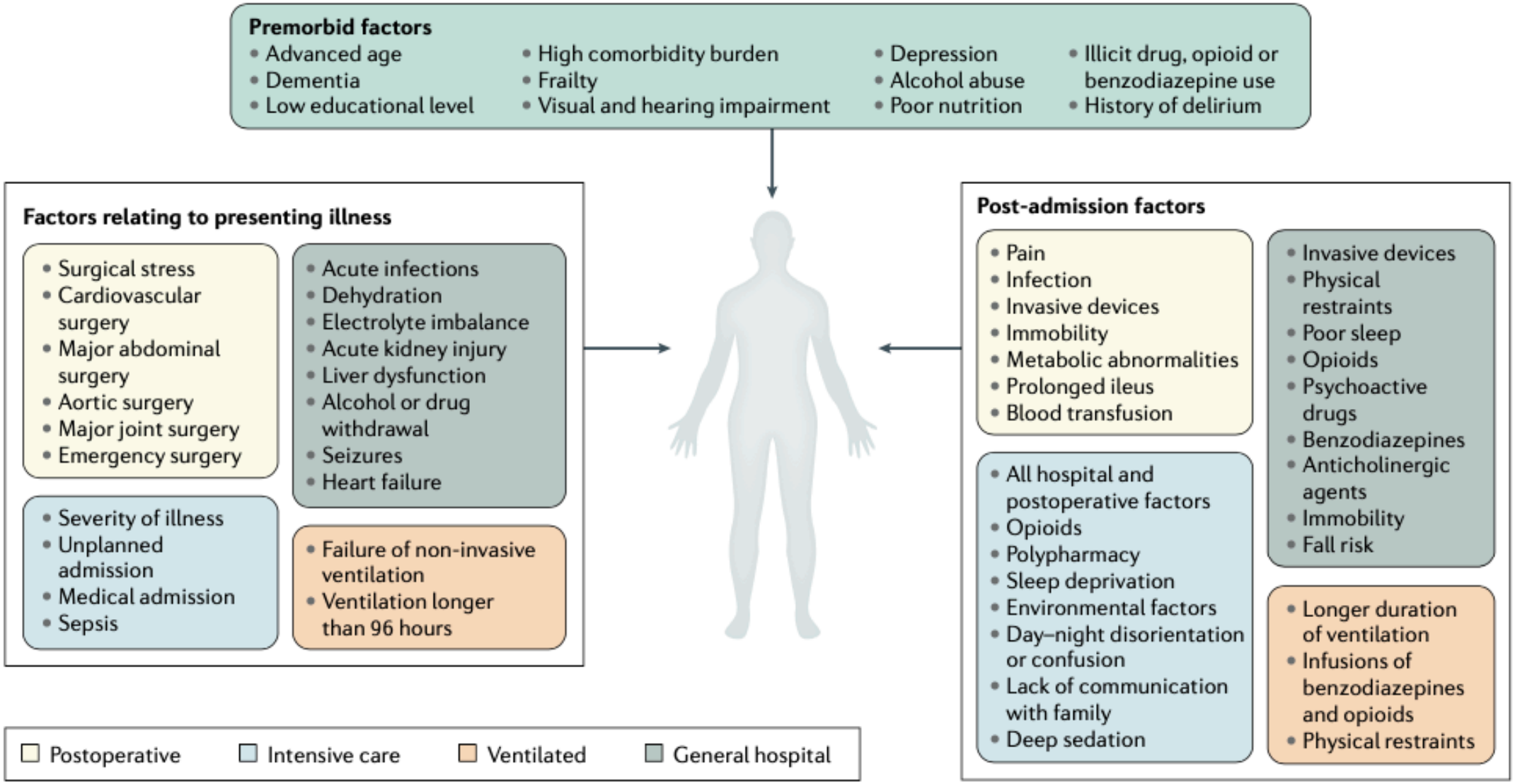
Common risk factors



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Diagnosis : History

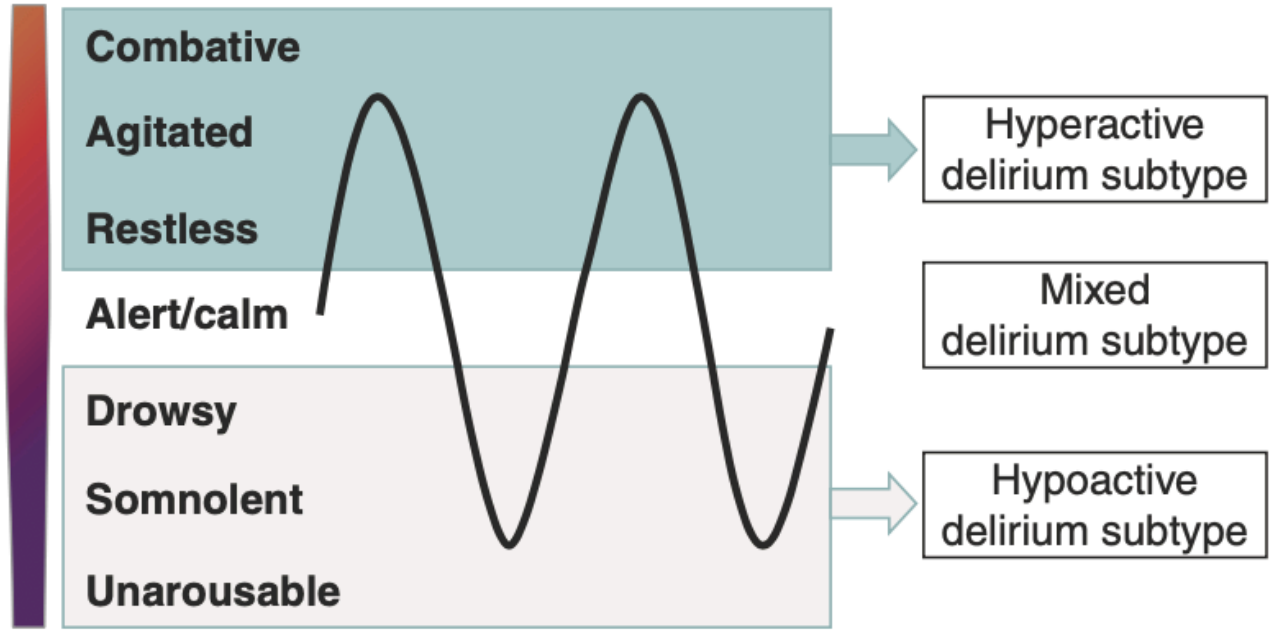
One key element :

→ **Determining the timeline** of the mental status changes.

Other essential element :

Fluctuations in mental status :

patient seeming normal at times and very confused at others



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Diagnosis : Examination

Physical examination	
General medical examination, focusing on cardiac, pulmonary, and neurologic elements	Provides clues to causes of delirium; remember to look for transdermal patches
Cognitive examination, including attention testing (see the Box: Commonly Used Tests of Attention)	Inattention is the hallmark cognitive deficit in delirium; patients with Lewy body dementia may have symptoms at baseline that are similar to dementia (behavioral disturbances, fluctuating course); even in these patients, an acute change should be evaluated and managed as delirium

One key element :

→ Determining the level of consciousness and attention

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Diagnosis : Examination

Commonly Used Tests of Attention

- Digit span (up to 5 forward and 4 backward)
- Recite the days of the week and the months of the year in reverse order
- Continuous performance task (instruct patient to raise hand when he or she hears a certain letter in a list)
- Attention screening examination (show pictures; ask patient to remember and recall)
- Recite a list of serial 7's or 3's
- Spell "world" backward

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Table 2 | Tools for the assessment of delirium

Tool	Description	Reference
CAM	Most widely used screening test for the presence of delirium; a four-item instrument based on DSM-III-R delirium criteria, requires the presence of acute onset and fluctuating course, inattention, and disorganized thinking or loss of consciousness	Inouye *et al.* (1990)[52] Wei *et al.* (2008)[53]
CAM–ICU	Delirium is diagnosed when patients demonstrate an acute change in mental status or fluctuating changes in mental status, inattention measured with either an auditory or a visual test, and either disorganized thinking or an altered level of consciousness. Importantly, the CAM–ICU can only be administered if the patient is arousable in response to a voice without the need for physical stimulation	Ely *et al.* (2001)[113] Ely *et al.* (2001)[114]
DRS-R98	16-item scale, including 13 severity items and 3 diagnostic items. Severity scores range from 0 to 39, with higher scores indicating more-severe delirium; delirium typically involves scores ≥15 points	Trzepacz *et al.* (2001)[115]
DSI	A structured interview detects the presence or absence of seven DSM-III criteria for delirium; delirium is said to be present if disorientation, perceptual disturbance or disturbance of consciousness have presented within the past 24 h	Albert *et al.* (1992)[116]
MDAS	Measures delirium severity on a 10-item, four-point observer-rated scale with scores that range from 0 to 30	Breitbart *et al.* (1997)[54]
NEECHAM Confusion Scale	Nine scaled items divided into three subscales: subscale I, information processing (score range 0–14 points), evaluates components of cognitive status; subscale II, behavior (score range 0–10 points), evaluates observed behavior and performance ability; subscale III, performance (score range 0–16 points), assesses vital function (that is, vital signs, oxygen saturation level and urinary incontinence). Total scores can range from 0 (minimal function) to 30 (normal function). Delirium is present if the score is ≤24 points	Neelon *et al.* (1996)[117]
ICDSC	Bedside screening tool for delirium in the intensive care unit setting; eight-item checklist based on DSM-IV® criteria, items scored as 1 (present) or 0 (absent); a score ≥4 points indicates delirium	Bergeron *et al.* (2001)[118]
Cognitive Test for Delirium	Can be used with patients unable to speak or write; assesses orientation, attention, memory, comprehension and vigilance, primarily with visual and auditory modalities. Each individual domain is scored 0–6 in two-point increments, except for comprehension, which is scored in single-point increments. Total scores range from 0 to 30, with higher scores indicating better cognitive function	Hart *et al.* (1997)[119] Hart *et al.* (1996)[120]

Abbreviations: CAM, Confusion Assessment Method; CAM–ICU, Confusion Assessment Method–Intensive Care Unit; DRS-R98, Delirium Rating Scale; DSI, Delirium Symptom Interview; DSM, Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, Arlington, VA); ICDSC, Intensive Care Delirium Screening Checklist; MDAS, Memorial Delirium Assessment Scale.

Tamara G. Fong, et al.Nature reviews, Neurology (2009)

Differential diagnosis

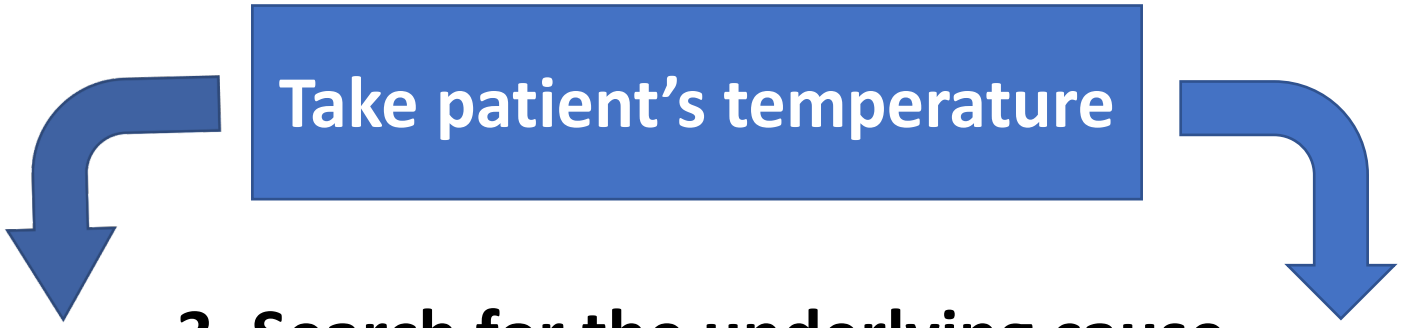
Table 1 | Differentiating features of conditions that mimic delirium

Feature	Condition			
	Delirium	**Alzheimer disease**	**Psychotic disorders**	**Depression**
Descriptive features	Confusion and inattention	Memory loss	Loss of contact with reality	Sadness, anhedonia
Onset	Acute	Insidious	Acute or slow	Slow
Course	Fluctuating, often worse at night	Chronic, progressive (but stable over the course of a day)	Chronic, with exacerbations	Single or recurrent episodes; can be chronic
Duration	Hours to months	Months to years	Months to years	Weeks to months
Consciousness	Altered	Normal	Normal	Normal
Attention	Impaired	Normal, except in late stages	May be impaired	May be impaired
Orientation	Fluctuates	Poor	Normal	Normal
Speech	Incoherent	Mild errors	Normal or pressured	Normal or slow
Thought	Disorganized	Impoverished	Disorganized	Normal
Illusions and hallucinations	Common (often visual)	Rare, except in late stages	Common	Not usually
Perceptions	Altered	Altered or normal	Altered	Normal
Psychomotor changes	Yes	No	Yes	Yes
Reversibility	Usually	Rarely	Rarely	Possibly
EEG reading	Moderate to severe background slowing	Normal or mild diffuse slowing	Normal	Normal

Confusional state in practice

In the emergency room :

1. Diagnostic of confusional state
2. Rule out differential diagnoses



3. Search for the underlying cause

Confusional state with fever

Confusional without fever

Confusional state in practice

Etiology

Confusional state with fever

1. **CNS infections :** E.g.

Neurological complications of Malaria
Herpes, West Nile
MIS-C Post SARS-CoV-2

2. Neuroleptic malignant syndrome
3. An infection outside the CNS in a patient with a brain disease (e.g., dementia)

Confusional without fever

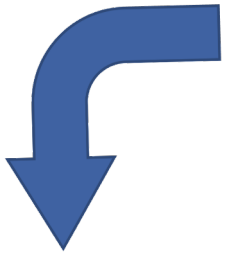
1. **Toxic, Iatrogenic**
2. **Epilepsy**
3. **Metabolic**
4. **Vascular :**

SDH, Stroke

5. Prion disease
6. Auto-immune encephalitis
7. Degenrative diseases : DLB

Confusional state in practice

Etiology



Confusional state with fever

1. **CNS infections :** E.g.
Neurological complications of Malaria
Herpes, West Nile
MIS-C Post SARS-CoV-2
2. **Neuroleptic malignant syndrome**
3. **An infection outside the CNS in a patient with a brain disease (e.g., dementia)**

- **Laboratory assessment : CBC, C-reactive protein, +/- CK**
- **CT scan or brain MRI**
- **Lumbur puncture**
- **Other infectious work-up: Chest radiography, urinalysis, culture**

Confusional state in practice

Etiology

- History
- Examination
- Basic laboratory tests (CBC, iono, liver)
- EEG
- CT Scan, Brain MRI
- Anti-neurone antibodies
- CSF analysis (Anti-neuronal Ab, CSF Ig)

Confusional without fever

1. Toxic, Iatrogenic
2. Epilepsy
3. Metabolic
4. Vascular :
   SDH, Stroke
5. Prion disease
6. Auto-immune encephalitis
7. Degenrative diseases : DLB

Confusional state in practice

1. History
2. Examination
3. Clinical investigations

Targeted laboratory evaluation (*selected* tests based on clues from history and physical)	Based on history and physical examination, *consider*: • Laboratory tests: CBC, electrolytes, calcium, glucose, renal function, liver function, thyroid function, urinalysis, cultures of urine, blood, sputum, drug levels, toxicology screen, ammonia level, vitamin B12 level, cortisol level • Arterial blood gas • Electrocardiography • Chest X-ray • Lumbar puncture reserved for evaluation of fever with headache, and meningeal signs, or suspicion of encephalitis
Targeted neuroimaging (*selected* patients)	• Assess focal neurological changes, since stroke can present as delirium • Suspicion of encephalitis for temporal lobe changes • History or signs of head trauma
Electroencephalography (*selected* patients)	• Evaluate for occult seizures • Differentiate psychiatric condition from delirium

Inouye et al. Lancet. 2014

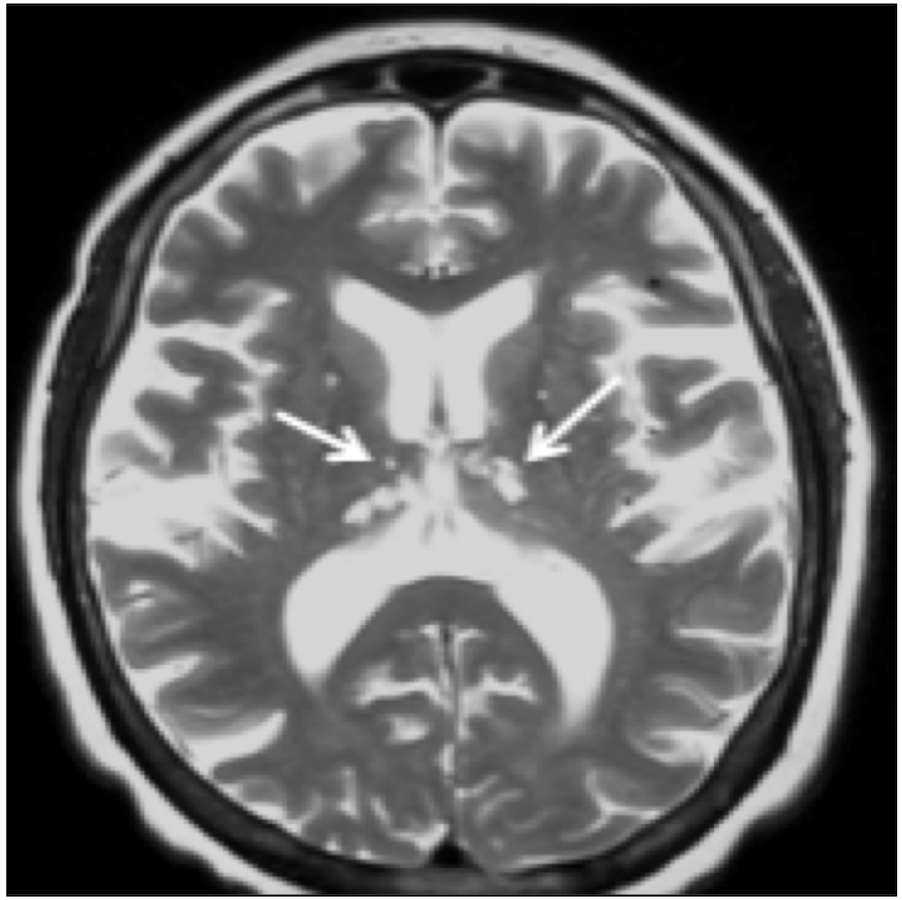
Case 1

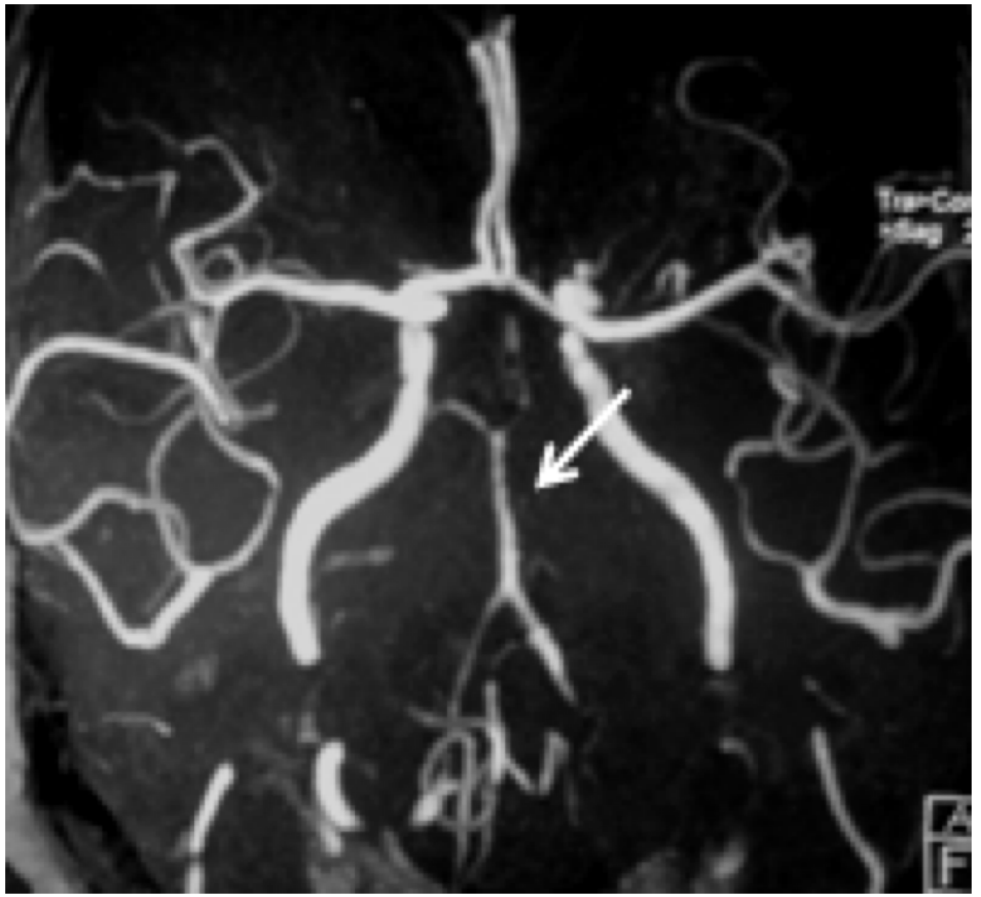
Mrs , 49 yo

- A woman aged 49 years old
- from Congo
- 3 months after a malarial attack: alteration of consciousness + generalized epileptic seizure
- Laboratory tests: hepatic cytolysis and leukolymphopenia
- Normal brain CT scan

Case 1

Mrs , 49 yo





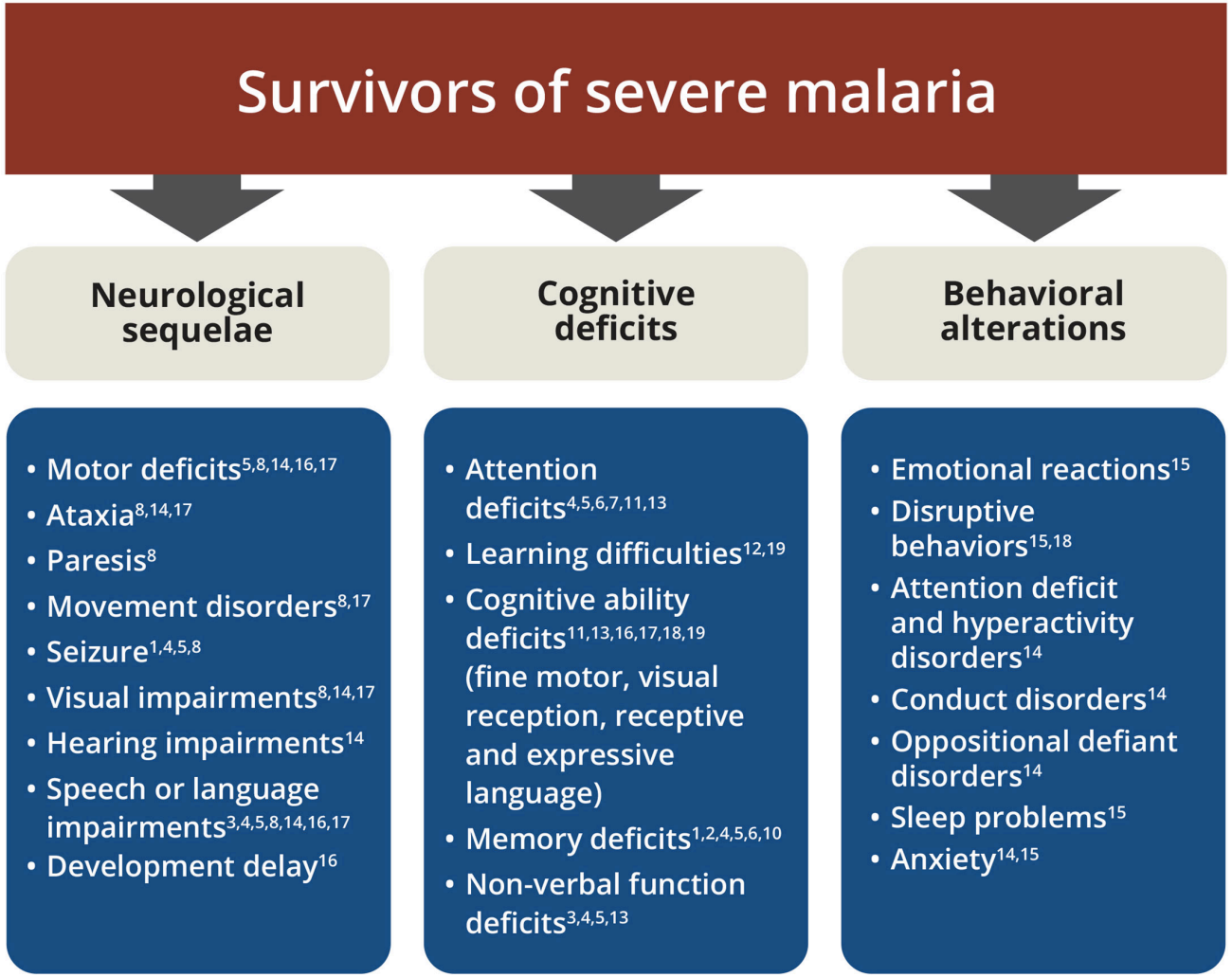
- **Smear examination -> severe malarial attack**

Neurological complications of Malaria

Cerebral malaria

Additional neurological manifestations :

- **Posterior reversible encephalopathy syndrome (PRES) reversible cerebral Vasoconstriction syndrome (RCVS)**
- **malarial retinopathy**
- **Post-malarial neurological syndrome (PMNS)**
- **Acute disseminated encephalomyelitis (ADEM**
- **Guillain-Barré syndrome (GBS)**
- **Cerebellar ataxia**



Trivedi, S, Chakravarty, *Curr Neurol Neurosci Rep* (2022)
Pamela Rosa-Gonçalves, Front. Cell. Infect. Microbiol. (2022)

Case 2 Mrs FDA, 78 yo

- Medical history: high blood pressure, dyslipidemia, thyroid disorder
- Parkinson's disease stable for 3 years on **Modopar 250, melatonin, paroxetine**
- **Worsening of motor symptoms** in May 2023: started on **amantadine 200 mg/day,** leading to the **emergence of psychobehavioral disturbances**, followed by **amitriptyline**
- **Worsening symptoms**: **visual hallucinations, impaired vigilance, sleep disturbances**
- Fell and fractured the femoral neck
- Paroxysmal episode of abnormal movements and screams, followed by generalized hypotonia and gradual awakening → **Levetiracetam 125 mg/day** (**received 750 mg/day)**

Case 2 Mrs FDA, 78 yo

Neurological examination :

- Somnolent, Glasgow Coma Scale (GCS) score = 13
- Temporo-spatial disorientation
- Parkinsonian syndrome Blood tests: CBC, C-reactive protein, ionogram, transaminases, and thyroid-stimulating hormone were all within normal limits.
- Normal brain MRI

EEG : Triphasic waves, delta slowing

Toxic/iatrogenic causes of confusional state

- **Alcoholism :** alcoholic intoxication, alcoholic hallucinosis, delirium tremens, abrupt withdrawal
- **Psychoactive substances. :** cannabis; high-dose ether, solvents, hallucinogens, amphetamines, barbiturates, opioids
- **Occupational or accidental poisoning. :** carbon monoxide, lead, arsenic
- **Medication poisoning** (especially in the elderly), antidepressants, anticholinergics, benzodiazepines, lithium, corticosteroids, antibiotics.

Table 2. **Drugs That May Cause Delirium and Potential Substitutes•**

Agent	*Potential Mechanism Leading to Delirium*	*Potential Substitute*	*Notes*
Benzodiazepines (long- and short-acting)	CNS sedation	Nonpharmacologic sleep management; if required for patient safety, use short-acting in smallest effective dose	May be required for sedation in critical care setting; associated with precipitation of or worsening delirium
Alcohol	CNS sedation	If history of regular/significant intake, consider withdrawal syndrome and treat appropriately	–
Antidepressants (the tertiary amine tricyclic agents: amitriptyline, imipramine, doxepin)	Anticholinergic toxicity	Should be reserved for patients who do not respond to first-line treatment with SSRIs or SNRIs	–
Antihistamines, especially first-generation (e.g., diphenhydramine)	Anticholinergic toxicity	Nonpharmacologic sleep protocol; alternative decongestant strategies	Often included in over-the-counter preparations for sleep
Anticholinergics: bladder antispasmodics	Anticholinergic toxicity	Consider behavioral interventions	Newer agents may have fewer CNS adverse effects
Opioid analgesics	Anticholinergic toxicity, CNS sedation, constipation	Opiate-sparing analgesic regimens; use the lowest effective dose (opioid metabolites can accumulate in renal impairment) and provide supportive measures (e.g., to prevent constipation)	–
Antipsychotics	Anticholinergic toxicity, CNS sedation	Avoid use altogether; if use is necessary for patient safety and care delivery, use lowest effective dose	Discuss risks and potential benefits with patient or surrogate decision maker
Antibiotics, especially fluoroquinolones	GABA and NMDA receptor effects	Choose alternative antimicrobial agent when possible	Can also be associated with hypoglycemia, which may worsen delirium

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Case 3

Mr, 78 yo

- 67-year-old man, a farmer,
- Medical history : ?
- Brought to the emergency room after an evening. He was:
  - Disoriented in time and space
  - Calm, perplexed, slowed down
  - Without neurological signs of localization or fever

→ Diagnosis?

Case 3

Mr, 78 yo

- Brother's interview:

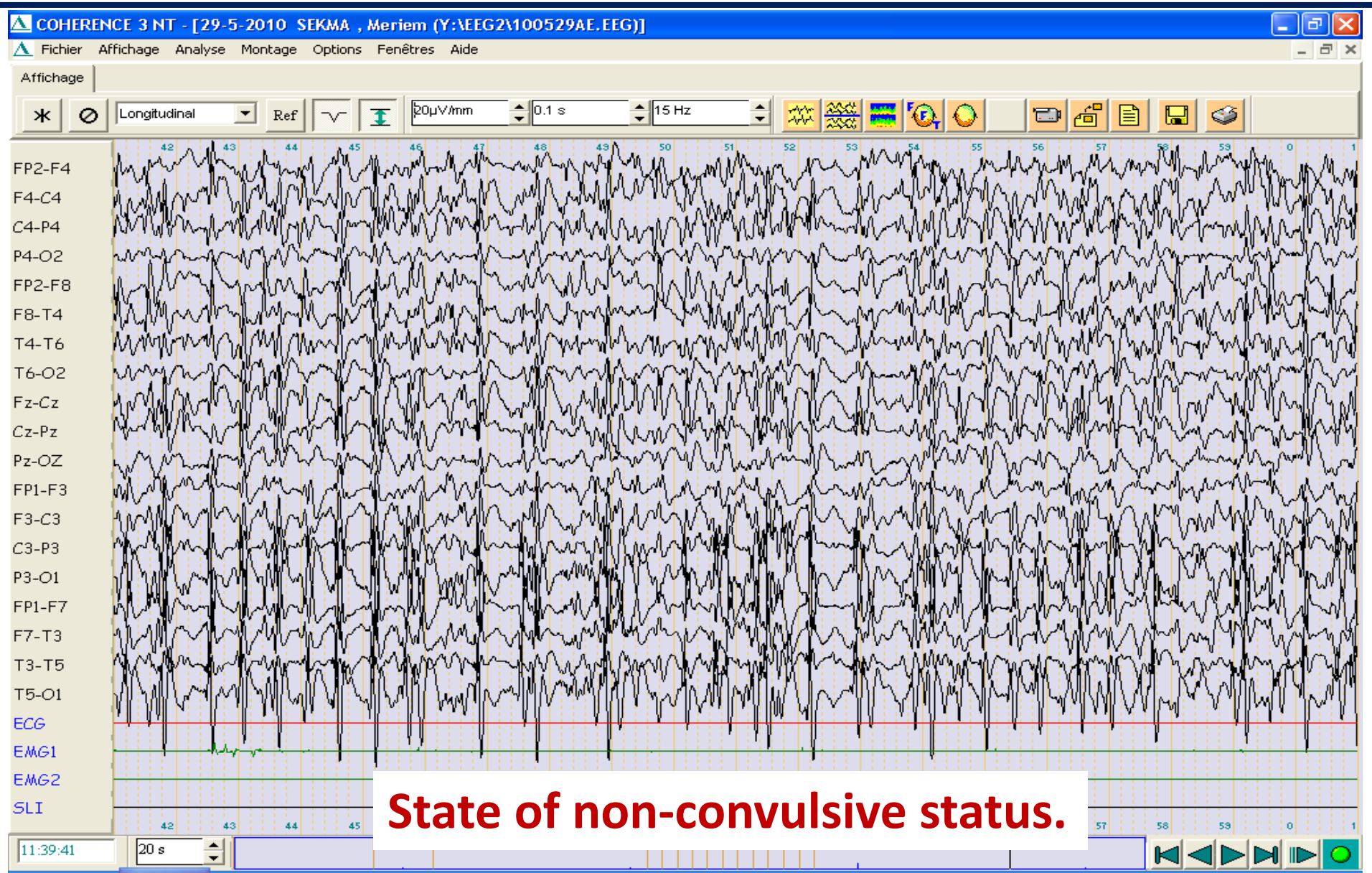
The patient has been taking Depakine for a week due to epilepsy.

- Diagnosis?

1. Postictal confusion
2. Non-convulsive status epilepticus
3. Drug/toxic encephalopathy

Case 3

Mr, 78 yo



State of non-convulsive status.

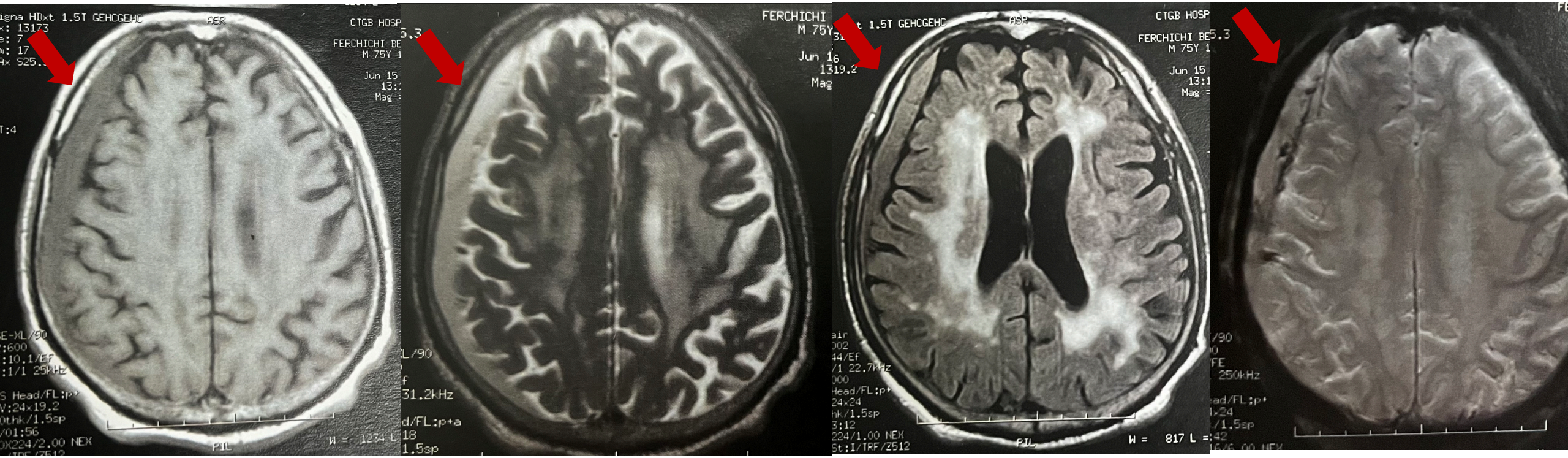
Case 4

Mr BF, 75 yo

- Medical history: Lung cancer /chemotherapy
- 5 months ago : rapid onset of behavioral disturbances
- Neurological examination :
  - Confusion
  - Pyramidal syndrome
  - Cerebellar syndrome

Case 4

Mr BF, 75 yo



Chronic subdural hematoma

Key Recommendations of the NICE Guideline for Delirium

- Assess delirium risk factors when patients are admitted to the hospital, especially those aged ≥65 years, those with cognitive impairment, those with a current hip fracture, and those with severe illness
- Prevent delirium by addressing risk factors using a tailored multicomponent intervention
- Screen for incident delirium by assessing recent changes or fluctuations in cognitive function, perception, physical function, and social behavior on ad- mission and at least daily thereafter
- Diagnose delirium using a clinical assessment based on formal criteria and conducted by a trained health care professional; document in the medical record
- Manage delirium by:

Identifying and managing possible causes

Ensuring effective communication and reorientation and providing reassurance

Considering the involvement of family, friends, and caregivers

Providing care in a suitable environment

If a person with delirium is distressed or is a risk to themselves or others:

- Use verbal and nonverbal deescalation techniques, such as quietly sitting at the bedside and engaging the patient in conversation or playing relaxing music
- If these are not effective or appropriate, consider short-term (usually ≤1 week) haloperidol at the lowest clinically appropriate dose and titrate cautiously according to symptoms
- Avoid using antipsychotic drugs if possible in patients with Parkinson disease or Lewy body dementia

Management

- **Symptomatic treatment**

- ***Nonpharmacological acute treatment strategies*** : first-line treatments for all patients. It include reorientation and behavioral intervention

- ***Pharmacological therapy***

- Antipsychotics (neuroleptics)
- Benzodiazepines
- Trazodone

- **Etiological treatment**

Management

Table 3 | Pharmacological therapy for delirium

Drug	Dose	Adverse effects	Comments
Acute therapy			
Antipsychotics[a]			
Haloperidol	0.5–1 mg PO or IM; can repeat every 4 h (PO) or every 60 min (IM)	Extrapyramidal syndrome, prolonged QT interval	Randomized, controlled trials demonstrate reduction in symptom severity and duration[81,82]
Atypical antipsychotics[a]			
Risperidone	0.5 mg BID	Extrapyramidal syndrome, prolonged QT interval	Randomized, controlled trials comparing efficacy against haloperidol showed comparable response rates[82–84]
Olanzapine	2.5–5 mg daily		
Quetiapine	25 mg BID		
Benzodiazepines[b]			
Lorazepam	0.5–1 mg PO; can repeat every 4 h	Paradoxical excitation, respiratory depression, excessive sedation, confusion	Did not show improvement in condition; treatment limited by adverse effects[81]
Cholinesterase inhibitors[c]			
Donepezil	5 mg QD	Nausea, vomiting, diarrhea	No randomized, controlled studies have been conducted; some case studies have indicated promise[63–65]
Prophylactic therapies (potential)[c]			
Antipsychotics			
Haloperidol	0.5–1 mg PO or IM; can repeat every 4 h (PO) or every 60 min (IM)	Extrapyramidal syndrome, prolonged QT interval	Use in surgical cases may reduce delirium incidence;[59] needs to be confirmed in additional studies
Cholinesterase inhibitors			
Donepezil	5 mg QD	Nausea, vomiting, diarrhea	Prevention studies have not demonstrated efficacy[61,62]

[a]Antipsychotics are the most widely used drugs for the treatment of delirium-related agitation but can have marked adverse effects. [b]Benzodiazepines should be reserved for treatment of drug withdrawal, diffuse Lewy body disease, or as second-line treatment following failure of antipsychotics. [c]Not currently accepted clinical therapies. Abbreviations: BID, twice daily; IM, intramuscularly; PO, *per os* (by mouth); QD, once daily.

Fong, T. G. *et al. Nat. Rev. Neurol.* 5, 210–220 (2009)

Prevention of delirium

Table 2 Recommendations for the prevention of delirium

Prevention of delirium
Avoid causal factors: unnecessary hospitalization, polypharmacy
Timely recognition of prodromal symptoms: agitation, vivid dreams, insomnia, hallucinations
If inpatient admission is necessary, the patient should receive qualified geriatric care right from the start, i.e., in perioperative management
Dementia patients should be offered constant accompaniment by their family or other close caregivers ("sitters")
Consistent delirium screening, assessment of dementia, depression, anxiety disorders, addictive disorders (alcohol, benzodiazepines, nicotine), identification of history of delirium, geriatric consultation, and medication review are recommended
Minimizing stress, giving time for questions, and optimal pain management are also recommended for the perioperative setting

Key messages

- Confusional state ≃ Delirium
- Diagnostic : History and Examination
- Search for Risk factors
- Investigations : with and without fever
- Management : symptomatic and etiological