Delirium in Palliative Medicine

Sorting out the confusion?

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Delirium means to get off the track..

In latin: lira = track, de = from, out

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Delirium: what is it?

- Delirium is a serious neurocognitive syndrome
  - «acute brain failure»
  - global cerebral dysfunction
- Occurs commonly in older populations
- And in cancer patients
  - especially with advanced disease
  - and in the last hours of life

Definitions

- Most commonly used: American Psychiatric Association; Diagnostic and Statistical Manual
  - 2013: **DSM 5**
- WHO's International Classification system of Diseases, 11th revision **(ICD 11**), (Version: 04 / 2019)
  - Delirium
    - Due to disease classified elsewhere
    - Due to psychoactive substances
    - Due to multiple etiological factors
    - Due to unknown factors

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Definition DSM 5

- A disturbance in
  - **attention** (reduced ability to direct, focus, shift and sustain attention)
  - **awareness** (reduced orientation to the environment) - changed from consciousness in DSM IV
- The disturbance
  - develops over a **short period of time** (hours to a few days)
  - represents a **change** from baseline, and tends to **fluctuate**
- An additional disturbance in **cognition**
  (memory deficit, disorientation, language, perception)

Definition DSM 5

- The disturbances above
  - are **not better explained by another preexisting**, established neurocognitive **disorder**
  - and do not occur in the context of e.g. coma
- 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
  - **or** is due to **multiple etiologies**

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Epidemiology

- Incidence and prevalence rates vary widely
  - Due to differences in: Populations, definitions, assessment tools, staff training
- The prevalence increases from admission, during inpatient stay and towards the last weeks or hours preceding death
  - Studies screening participants at least daily reported higher incidence
- The hypoactive form (to be discussed later..) seems to the most prevalent form, but also frequently misdiagnosed

Epidemiology

- From a systematic review, palliative care settings (2019)
  - 42 studies (34 studies with cancer patients)
  - Only on study had an overall low risk of bias
  - Subtypes reported in 11 studies
- Point prevalences:
  - 4-12% in community settings
  - 6-74% in inpatient palliative care units
  - 42-88% at the end of life
  - Pooled point prevalence on admission: 35% (95% CI 29-40%, n=14)
- Subtypes
  - Hypoactive form: 39% (range 22-86%)
  - Hyperactive form: 14% (range 0-33%)
  - Mixed delirium: 23% (range 10-45%)

Mortality and morbidity

- Delirium is associated with increased post-discharge mortality
  - Hazard ratio (HR) 2.0 (95% CI 1.5-2.5)
- Delirium is associated with post-discharge institutionalisation
  - Odds ratio (OR) 2.4 (95% CI 1.8-3.3)
- Estimates in oncological settings vary widely (different contexts and settings)
- Nonetheless: associations between delirium and adverse outcomes are evident

Risk factors

- Risk factors for delirium are often described as
  - Predispoing factors (baseline vulnerability)
  - Precipitating factors (responsible for directly activating the delirium)
- Patients with high baseline vulnerability are more prone to develop delirium
- Patients with low baseline vulnerability are more resistant to the development of delirium

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Risk factors

- In advanced stage cancer:
  - Distinction between predisposing and activating factors more arbitrary
  - Due to multifactorial etiology and overall comorbidity
- However:
  - Many risk factors are common
  - And even in advanced malignancies potentially reversible

Risk factors

- Cancer-related factors
  - CNS tumores, brain metastases, meningeal metastases
- Toxicities from anticancer treatments
  - Radiotherapy or systemic anticancer treatments
- Physical complications in cancer patients
  - Electrolyte abnormalities, infections, nutritional deficiency (e.g. vitamins), dehydration, seizures
- Medications
  - Opioids, anxiolytics, corticosteroids, anticholinergics, anticonvulsants, antipsychotics, polypharmacy
- Others
  - Age, dementia, hearing & visual impairment, constipation, urinary retention, alcohol or drug abuse or withdrawal (nicotine included), organ failure (brain, liver, renal, cardiac, endocrinopathy)

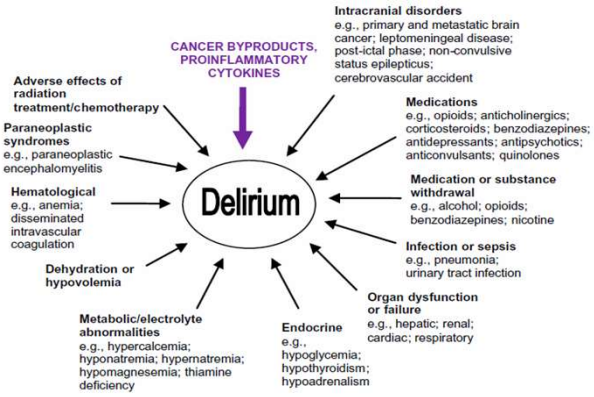
Pathophysiology

- Multifactorial and not well understood, unlikely that a single cause or mechanism will be discovered
- Several sets of interacting biological factors
- ⟶Disruption of large scale neuronal networks

- Postulated contributors include
  - neurotransmitters (eg.**decrease** in acetylcholin and **increase** in dopamin, but also on a broader level)
  - neuroinflammation with blood-brain barrier dysfunction
  - neuronal aging, hypercortisolism, hypoxia, impaired glucose oxidation, electrolyte disorders

Etiology and pathophysiology: summing up

Fig. 3 Factors contributing to delirium in cancer patients (adapted from Bush and Bruera [160], with permission from the publisher)



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Etiology, pathophysiology and clinical presentation: at a glance

- Delirium occurs
  - when physical factors (often multiple occuring simultaneously)
  - act on a physiologically vulnerable brain

- Leading to
  - Confusion
  - Changes in perception
  - Altered behaviour

Clinical features of delirium

- Prodromal features
  - Anxiety, restlessness, irritability, disorientation, sleep disturbances

- Cognitive disturbance
  - Impaired attention and awareness (changed from baseline)
  - Disturbance in level of arousal
  - Reduced concentration and disorganised thought process
  - Impaired immediate recall and memory
  - Visospatial dysfunction
  - Language disturbance and incoherent speech

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Clinical features of delirium

- Perceptual disturbance and delusions
  - Hallucinations (usually visual or tactile), delusions, illusions and misinterpretations
- Psychomotor disturbance
  - Hypoactive delirium: Reduced psychomotor activity (movement, speech)
  - Hyperactive delirium: Agitation, restlessness, increased flow of speech, easily startled
  - Mixed delirium: unpredictable, fluctuating features of both hypo- and hyperactivity
  - (Terminal delirium)
- Sleep-wake circle disturbance
  - Insomnia and reversal of sleep-wake cycle with daytime somnolence
  - Distressing dreams and nightmares
  - Nocturnal worsening of symptoms

Clinical features of delirium

- Emotional disturbance
  - Fear and anxiety
  - Irritability and emotional lability with euphoria and apathy
  - Depression and withdrawal
- Neurological abnormality
  - Tremor and myoclonus
  - Apraxia and aphasia
- Timeline
  - Usually rapid development (hours to few days)
  - Fluctuation of severity (often increasing in the evening and nighttime)
  - Lasting about one week? (excl. actively dying pts.), but may persist (older pts.)

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Clinical assessment, diagnosis and screening

- Fluctuation in symptoms and hypoactive presentation may complicate the process

- History with comparent information (staff and relatives)
- Clinical examination with emphasis on predisposing and precipitating factors
  Baseline function? Medication?

- Targeted laboratory assessment, including blood and urine
- Radiography – Chest? Brain??
- ECG?

- What about a validated instrument for the identification of delirium?

Instruments for identification of delirium

- A variety of tools have been developed, but few validation studies

- The CAM (Confusion Assessment Method) is widely used
- The CAM is translated to at least 12 languages
- Operational approach to the diagnostic criteria

- Described 82% sensitivity and 99% specificity (all populations)
- However:
  - Only one population where the majority was cancer patients
  - And selection bias (not representative for the entire cancer population)

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CONFUSION ASSESSMENT METHOD (CAM)

	yes	no
1. **ACUTE ONSET/FLUCTUATING COURSE** Is there a history of an acute change in mental status with evidence of fluctuation in the degree of symptoms?	___	___
2. **INATTENTION** Does the patient have difficulty focusing attention (e.g., being easily distractible, or failing to focus on the discussion or sustain an effort)?	___	___
3. **DISORGANIZED SPEECH** Is the patient's speech disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching of subjects?	___	___
4. **ALTERED LEVEL OF CONSCIOUSNESS** Is the patient's level of alertness either hyperalert (e.g., vigilant, overly sensitive to environmental stimuli, easily startles); or hypoalert (e.g., lethargic, stuporous, drowsy, difficult to arouse)?	___	___

Diagnosis requires the presence of features 1 and 2 and either 3 or 4.

ESMO Guideline recommendations (2018)

- The diagnosis of delirium should be made using a clinical assessment based on DSM or ICD criteria
  - The evidence is insufficient to recommend for or against diagnostic tools
- The evidence is insufficient to recommend the routine use of screening tools for delirium in cancer patients
  - No high quality evidence
  - Screening potentially offers benefits, but also harm
  - Due to high incidence, at least daily observations of inpatients
- The evidence is insufficient to recommend for or against routine use of tools to assess delirium severity

Differential diagnoses

- Mania and other psychosis: often previously known, delusions highly systematized and the sensorium otherwise clear
- Depression: may have cognitive symptoms, but less fluctuation and dysphoria present
- Dementia: gradual reduction in cognition, no disturbance of attention or alertness- except in the most severe cases

Management of precipitating factors of delirium (ESMO recommendations)

- Opioid switch (dose, type, administration) may be appropriate
- Limited evidence for the role of assisted hydration
- Treating infections in accordance with goals of care
- Bisfosfonates for hypercalcemia
- Management of SIADH (e.g. discont. drugs, fluid restriction or oral salt intake)
- Magnesium replacement for hypomagnesemia
- Medication or therapy withdrawal when delirium due to cancer treatment

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Multicomponent non-pharmacological interventions for delirium

may include

- Individualised care
- Checklists
- Reorientation
- Attention to sensory deprivation
- Familiar objects
- Cognitive stimulation
- Nutrition/hydration
- Identification of infections
- Mobilisation
- Sleep hygiene
- Oxygenation
- Electrolytes
- Multi disciplinary teams
- Pain control
- Medication review
- Bowel and bladder care
- Mood
- Focus on postoperative complications

Non-pharmacological interventions for the prevention and treatment of delirium (ESMO)

- Multicomponent non-pharmacological interventions may prevent delirium in inpatients (by around on third?)
- Including reorientation strategies, maintain safe mobility, normalise sleep-wake cycle

- However:
  - A striking paucity of high-quality evidence for cancer patients

- Thus, for adult cancer patients:
  - For most non-pharmacological interventions:
    - No evidence to base recommendations
  - Assisted hydration is not more effective than placebo for the prevention of delirium

Pharmacological interventions for the *prevention* of delirium in adults with cancer (ESMO)

- Given the absence of studies evaluating pharmacological prevention of delirium:
  - no evidence-based recommendations are proposed
- Based on available evidence:
  - Deprescribing appear to be worthwhile in older patients
  - Insufficient data to support this recommendation for all cancer patients

Pharmacological interventions for the treatment of delirium in adults with cancer (ESMO)

- Opioid rotation (to fentanyl or methadone) is efficacious if opioid-associated delirium
- Haloperidol or risperidone has no demonstrable benefit in the symptomatic management of mild-to-moderate delirium and is not recommended in this context
- Drugs which may offer benefit in the symptomatic management of delirium, and appear to be less prone to extrapyramidal side effects than first generation antipsychotics:
  - Olanzapine
  - Quetiapine
  - Aripiprazole
- Methylphenidate may improve cognition in hypoactive delirium
- Benzodiazepines provide sedation and potential anxiolysis
  - Not considered part of the initial management
  - Pros and cons must be considered carefully

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NICE Guidelines
(Care for the adult dying)

- Consider a trial of an antipsychotic medicine to manage delirium or agitation
- Consider a trial of a benzodiazepine to manage anxiety or agitation
- BUT WE NEED MORE SPECIFIC TREATMENT ADVICE

Practical pharmacological management

- Many guidelines: haloperidol is the initial drug of choice
- 0,5-2,0 mg up to x 4 orally
- 0,5 mg intravenously every 30 minute until response
- Some evidence for up to 28 mg/24 h po
  - Review paper from 2015: up to 10 mg/d
  - More recent literature: up to 5 mg/24t, but higher doses if closely monitored
- Often administered subcutanously in a syringe driver
- If 5 mg/24h doesn't work, perhaps 10 or 15mg/24h will..
- Extrapyramidal side effects

Practical pharmacological management

- Second and third generation («atypical») antipsychotics should be considered effective alternatives to haloperidol

- Olanzapine (Zyprexa) 2,5-10 (20) mg/24h. Sedation the main dose-limiting adverse effect. Parenteral administration possible
- Quetiapine (Seroquel) 25-100 (300)mg/24h. Shorter half-life than olanzapine, easier to monitor. Sedating effect may be helpful

- Others (like risperidone, ziprazidone and aripiprazole)

Practical pharmacological management

- Sometimes agitation and restlessness may need treatment
- Midazolame much used in palliative care, often subcutanously in a syringe driver
- Some evidence for up to 10-30mg/24h

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