MUNI
PHARM

Cognitive disorders, BPSD, Delirium

Mild cognitive impairment- MCI

- an intermediate state between normal cognition and dementia
- Reflects: "cognitive impairment, no dementia„
- MCI is associated with the risk of AD and other neurodegenerative dementias

Definition:
„a measurable deficit in cognition in at least one domain, in the absence of dementia or impairment in activities of daily living“

Amnestic MCI - significantly impaired memory
Non-amnestic MCI - impairment in other domains – eg. executive functioning, language, or visual spatial skills

MCI - SYMPTOMS

Cognitive self-reported symptoms- primarily impaired memory

change over baseline
subjective memory complaints predicts cognitive decline
some difficulties with regard to memory normal in aging e.g. names, numbers
insensitive criterion - can reflect mood

Neuropsychiatric symptoms - behavioral problems, depression, irritability, anxiety, aggression, and apathy

Cognitive impairment may be a presenting symptom of depression, so-called „pseudodementia“
Vs.
Depression may also be an early manifestation of cognitive impairment

MCI - DIAGNOSIS

Clinical evaluation-interview
Neuropsychological testing
NeuroImaging

- Cognitive concern reflecting a change in cognition reported by patient or informant or observed by clinician
- Objective evidence of impairment in one or more cognitive domains, typically including memory
- Preservation of independence in functional abilities
- Does not meet criteria for dementia

MCI - DIFFERENTIAL DIAGNOSIS

(cerebro)vascular, traumatic, medical causes of cognitive decline must be excluded eg:

Psychiatric disorders - particularly depression, sleep disturbances
Adverse effects of medications
(eg. BZD., anticholinergic, antihistamine use)
Metabolic disturbances - particularly vitamin B12 deficiency and hypothyroidism
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Dementia

major neurocognitive disorder

Major dementia syndromes:

Alzheimer disease (AD)

- the most common form of dementia in the elderly, accounting for 60-80% of cases
- frequent concomitant cerebrovascular disease

Dementia with Lewy bodies

Frontotemporal dementia

Vascular (multi-infarct) dementia

Parkinson disease with dementia

Dementia - CLINICAL PRESENTATION

Problems with:

Retaining new information (eg, trouble remembering events)

Handling complex tasks (eg, credit cards)

Reasoning (eg, unable to cope with unexpected events)

Spatial ability and orientation (eg, getting lost in familiar places)

Language (eg, word finding)

Behavior

Informant interview:

- Problems with judgment
- Reduced interest in hobbies/activities
- Repeats questions, stories, or statements
- Trouble learning how to use a tool or appliance
- Forgetting the correct month or year
- Difficulty handling financial affairs (bill-paying, taxes)
- Difficulty remembering

Clinical dementia rating (CDR): 0, 0.5, 1, 2, 3

Impairment	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented or slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
Judgment and problem	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment to solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside of home; appears well enough to be taken to functions outside of family home	No pretense of independent function outside of home; appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self care	Fully capable of self care	Needs prompting	Requires assistance in dressing, hygiene keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impaired due to other factors.

Differential diagnosis of memory loss

Symptom	Usual cause	Examples
Gradual onset of short-term memory loss and functional impairment in more than one domain:	Dementia	Alzheimer disease, Parkinson dementia, Lewy body dementia, Pick's disease, alcohol-related dementia, Creutzfeld-Jacobs disease
I. Executive function (finances, shopping, cooking, laundry, transportation)		
II. Basic activities of daily living (feeding, dressing, bathing, toileting, transfers)		
Stepwise, sudden deterioration in cognition; episodes of confusion, aphasia, slurred speech, focal weakness	Cerebrovascular disease	Vascular dementia, multi-infarct dementia, Binswanger's dementia (subcortical dementia)
Acute cognitive impairment with clouded sensorium; difficulty with attention; may have hypersomnolence	Delirium	Hypo- or hyperglycemia, hypo- or hypernatremia, hypoxemia, anemia, intermittent cerebral ischemia, thyrotoxicosis, myxedema, alcohol withdrawal, sepsis, drugs (especially cholinergics, benzodiazepines, etc)
Complains of memory loss, decreased concentration, impaired judgment, feels worse in morning and hopeless	Depression	Minor depression, dysthymic disorder, major depression, pathologic grief reaction

Dementia

- medical illnesses and comorbidities exacerbating poor cognition are common in elderly patients with dementia
- frequently has more than one cause
- medication side effects - precipitating factor
- depression, and other central nervous system illnesses can be presented with cognitive impairment
- alcohol-related dementia

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Neuropsychological testing

usually involves extensive evaluation of multiple cognitive domains (eg, attention, orientation, executive function, verbal memory, spatial memory, language, calculations, mental flexibility and conceptualization)

Mini-Mental State Examination

most widely used cognitive test for dementia
tests a broad range of cognitive functions
scores can also be influenced by education

clock drawing task (CDT) and an uncued recall of three unrelated words

Treatment of MCI

Vascular risk factor modification

Patients with MCI and AD have a higher than expected prevalence of atherosclerosis risk factors – as suggested atherosclerosis risk factors should be treated aggressively

Pharmacological routine treatment of MCI nor recommended – lack of convincing benefit - controlled study support for this recommendation is not available

Nonpharmacological interventions

Treatment of dementia

Patients with (AD) have decrease in acetylcholine synthesis and impaired cortical cholinergic function

CHOLINESTERASE INHIBITORS - increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft
donepezil, rivastigmine, and galantamine – tbl., patches, solutions
Mild to moderate AD (MMSE 10-26)

Memantine - N-methyl-D-aspartate (NMDA) receptor antagonist, distinct and neuroprotective mechanism
Glutamate is the principal excitatory amino acid neurotransmitter acts at NMDA,
excessive stimulation can cause damage
moderate to severe AD (MMSE <17)

Treatment of dementia
-Other medication

Antioxidant therapy — Vitamin E (alpha-tocopherol 2000 IU daily) - modest benefit in delaying functional progression in patients with mild to moderate AD

Ginkgo biloba - evidence of benefit, variability in the dosing and contents of herbal extracts

Omega-3 fatty acids

Vitamins B

Neuropsychiatric symptoms of dementia

- prevalence increases with disease severity
- Behavioral disturbances commonly in the late afternoon or evening - phenomenon so-called as "sundowning
- Delusions are more common than hallucinations – esp. Paranoid

Agitation, aggression and other behavioral abnormalities - possible causes

- Pain
- Fear
- Confusion
- Poor sleep
- Medication toxicity
- Medical conditions – eg infections - Delirium

Delusions

Hallucinations

Depression

Anxiety

Euphoria

Aggression

Apathy

Irritability

Disinhibition

Wandering or pacing

Sleep disturbances

Pharmacotherapy

Behavioral and (Neuro)psychiatric symptoms of dementia (BPSD)

Delusions, Hallucinations - Pharmacotherapy is not necessary if symptoms do not trigger aggression, endanger the patient or others
Drugs to avoid — Benzodiazepines - only for acute stressful episodes

Severe or refractory symptoms - severe distress or safety issues:

Antipsychotics – atypical -agents of choice

- risperidone, quetiapine - should not be used routinely, may increase mortality

start with a low dose, and titrate slowly

Typical antipsychotics - no clear evidence of benefit for these agents in patients with dementia

- haloperidol may help control aggression, but not other neuropsychiatric manifestations of dementia

Melperone, tiaprid – indication in behavioral disturbances
safety profile more acceptable, comparable efficacy
Not available world-wide

Delirium and confusional states

among the most common disorders in older patients with medical illness

Delirium = Clinical syndrome:
essential components - disturbance of consciousness and altered cognition
incidence is higher in older age and pre-existing brain disease - dementia, stroke, or Parkinson disease; in patients with sensory impairment

Delirium

Delirium is usually acute or subacute in onset
associated with a clouding of the sensorium
fluctuations in the level of consciousness
difficulty maintaining attention and concentration

"acute confusional state" synonym to „delirium“
more general term "confusion„ - problem with coherent thinking
Confused patients in general are unable to think with normal speed, clarity, or coherence

DEFINITION AND TERMINOLOGY

Disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness
develops over a short period of time (usually hours to days) represents a change from baseline, and tends to fluctuate during the course of the day

Additional disturbance in cognition (memory deficit, disorientation, language, visuospatial ability, or perception)

The disturbances are not better explained by another preexisting, evolving or established neurocognitive disorder

Evidence from the history, physical examination, or laboratory findings that the disturbance is caused by:

- a medical condition
- substance intoxication or withdrawal
- or medication side effect

Additional features:
Psychomotor behavioral disturbances such as hypoactivity, hyperactivity with increased sympathetic activity, and impairment in sleep duration and architecture
Variable emotional disturbances, including fear, depression, euphoria, or perplexity.

EPIDEMIOLOGY

- primarily in hospital settings
- Nearly 30 percent of older medical patients experience delirium at some time during hospitalization
- In older surgical patients, the risk for delirium varies from 10 – more than 50%
  - intensive care units (70 %
  - emergency departments (10 %
  - hospice units (42 %)
- incidence is higher in older age and pre-existing brain disease - dementia, stroke, or Parkinson disease; in patients with sensory impairment

Pathophysiology of delirium and confusion

- poorly understood - highly unlikely that a single mechanism is involved
- multifactorial disorder
- Neurotransmitter and hormoral mechanisms
- Acetylcholine is the key neurotransmitter in the pathogenesis of delirium
- Alterations in other neurotransmitters are also present – e.g. GABA, serotonin, NA, D, endorfins

Possible causes of delirium
- in general any medical condition

Fluid and electrolyte disturbances (dehydration, elevated or depressed: sodium, calcium, magnesium, phosphate)

Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal

Infections (urinary tract, respiratory tract, CNS infection), fever-related delirium

Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal

Metabolic disorders (hypoglycemia, hypercalcemia, uremia, liver failure, thyrotoxicosis)

Low perfusion states (shock, heart failure), systemic organ failure

Postoperative states

Trauma

Brain disorders - Seizures

Nutritional - vitamin B12 deficiency, possibly folate and niacin deficiencies

Drugs or alcohol toxicity and withdrawal

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Drugs that cause or prolong delirium

Anticholinergics

Antihistamine drugs

Dopamine agonists

BZD, barbiturates

GIT agents – antiemetics..

Opioid analgesics

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Management of delirium principles

- Identifying and treating the underlying acute illness
- Avoiding factors known to cause or aggravate delirium, such as multiple medications, dehydration, immobilization, sensory impairment, and sleep disturbance
- Providing supportive and restorative care to prevent further physical and cognitive decline
- controlling dangerous and severely disruptive behaviors using low dose, short acting pharmacologic agents so the first three steps can be accomplished

Pharmacotherapy

- **<u>evidence does not support the use of psychotropic medications to prevent delirium</u>**
- **specific therapy of underlying condition - the most effective**
- **In the treatment of severe agitation or psychosis with the potential for harm - antipsychotics:**
- **effective alternatives are not available**
- **reduces the severity and duration of episodes**
- **Short term use only, patient monitoring essential**
- **long clinical experience with haloperidol, but of similar efficacy, and fewer side effects – quetiapine, risperidone, olanzapine at appropriate dosing**
- **Alternatives – melperone, tiaprid**

Benzodiazepines should be avoided – except for delirium in alcohol withdrawal syndrome
Cholinesterase inhibitors are not effective in preventing or treating the symptoms of delirium
Thiamine supplementation should be considered in all patients