Organic mental disorders

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Concept

- identified or highly supposed brain damage
  - direct - primary
  - secondary
    - the influence of other system malfunction on the central nervous system
      - = somatogenic, symptomatic
Weakness of this concept

- if these disorders are organic, does it mean that there is no brain dysfunction in the other ("not-organic", "functional") disorders

- while there is the chapter in ICD-10:
  - F00 - F09 Organic, including symptomatic, mental disorders
  - DSM-5 and ICD-11 have groups:
    - neurocognitive disorders
    - dementia
Etiology

- **direct damage to the brain**
  - trauma, tumor, degenerative changes, vascular disorders

- **secondary to a failure of another body system (s)**
  - e.g. endocrine disorders
  - inflammation
  - ionic imbalance - dehydration
  - hypoxia

- **exogenous causes**
  - intoxication and substance abuse - in a separate section
  - medicines (anticholinergics, stimulants)
Delirium

- around 15% of patients on postoperative / intensive units
  - significantly higher rate in elderly patients
- significantly increased risk of increased mortality in annual prospective follow-up
  - a sign of total body involvement and failure of regulatory functions
- very rarely of psychogenic origin
  - acute episode of a schizoaffective disorder
  - very serious psychotrauma
- basis - qualitative disturbance of consciousness
  - disorientation
  - a different degree of disintegration of psychic functions
  - disturbed memory encoding (even retrospective diagnosis)
- sign of global health problem and známka celkového postihnutia organizmu and failure of regulatory functions
Delirium or qualitative disturbances of consciousness
<table>
<thead>
<tr>
<th>Form - severity</th>
<th>Description</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>clouded</td>
<td>fluctuating attention, inaccurate orientation, slowing of mental functions</td>
<td>reorientation, activation, enhancing circadian rhythmicity (sleep) - antipsychotics in low doses at evening / night, consider nootropic at morning / lunch</td>
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<tr>
<td>consciousness</td>
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<tr>
<td>confusion</td>
<td>disorientation, jumps of association up to incoherent thinking, illusions, uneasiness, anxious mood</td>
<td>less incisive antipsychotics (tiaprid) also during the day I middle range of dosage, if intensive anxiety – consider temporary benzodiazepines</td>
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<tr>
<td>delirium</td>
<td>deeper disorientation, disintegration of mental functions, illusions, hallucinations with possible delusional interpretation, suggestibility, often resonant mood with possible aggression, emotions are influenced by hallucinations and delusions; • d. acutum grave or • furibundum - marked turmoil, hyperactive • d. blandum, musistans - without restlessness, hypoactive • occupational delirium • floccilation</td>
<td>higher doses of antipsychotics, more incisive (haloperidol), atypical antipsychotics for the control of hallucinations, delusions if there is a risk of extrapyramidal syndrome; combination with benzodiazepines (midazolam) in severe restlessness; physical restrain if needed</td>
</tr>
</tbody>
</table>
Psychopathology

- **leading symptoms - cognitive impairment**
  - memory
    - disturbance of the short-term memory
    - long-term memory and semantic memory can be relatively preserved
      - repetition of content in short period of time
  - thinking/speech disturbances
    - impaired recollection of words and problem with their proper use
    - phonological paraphasia to neologisms
    - circumlocution - a descriptive expression of the term
    - semantic paraphasia (car vs. carriage)
    - meaningful expression (loss of thread of information)
  - syntax - agramatisms, incoherence (anomic aphasia)
    - perseveration, verbigeration, palilalia
  - attention
    - sustained attention (concentration), distribution of attention
  - executive functions
    - inability to perform complex activities that require planning and a certain procedure and decision-making - a significant effect on functionality (ADL - activities of daily life)
    - apraxia
Further symptoms

- **non-cognitive symptoms**
  - neuropsychiatric or Behavioural and Psychological Symptoms of Dementia - BPSD
  - affectivity
    - depression (importance to differentiate *pseudodementia*)
    - anxiety
    - affective lability/irritability
    - „blund“ euphoria, apathy, moria, mania
  - perception
    - hallucination
    - misidentification
      - (Capgras and Fregoli syndrome – the border of thinking/perception disorder)
  - thinking
    - suspiciousness, paranoid delusions
  - disturbances of sleep-wake cycle
    - night wandering, in LBD disturbances associated with REM phase
  - „behavioral“
    - conduct disorders (often associated with organic change of personality)
      - inappropriate sexual behavior
  - physical symptoms
    - muscles atrophy, decrease of mobility, risk of failures
    - problems with feeding and change of weight
    - extrapyramidal signs
    - poruchy vylučovania až inkontinencia
Prevalence of dementia (England and Wells; BMJ 2017)
Dementia by age categories
(Anglicko a Wells; BMJ 2017)

Higher age longevity – higher incidence = age as the main risk factor
Classification of dementias

- **Primary degenerative**
  - Dementia in Alzheimer's Disease
  - Dementia with Lewy bodies
  - Frontotemporal dementia
  - Dementia in Parkinson's disease
  - Dementia in Huntington's Disease

- **Vascular**
  - MID (multi-infarct dementia)
  - Binswanger's disease
  - Dementia following a sudden stroke
  - Dementia in autoimmune brain vasculitis
Secondary dementias

Dementia in metabolic diseases:

Hereditary:
- Wilson's disease
- Acute intermittent porphyria

Non-hereditary:
- Uremic encephalopathy
- Hepatic encephalopathy

Dementia in endocrinopathies:
- Thyreopathy (hypothyroidism, thyrotoxicosis)
- Disturbances of parathyroid function
- Adrenal function disorders (Addison's disease, Cushing's syndrome)
- Hypoglycemia

Dementia based on infectious etiology:
- AIDS associated dementia (HIV dementia)
- Dementia in neurosyphilisation
- Dementia in Lyme borreliosis
- Progressive multifocal leukoencephalopathy
- Herpetic encephalitis
- Prionoses

Dementia in hypovitaminoses:
- Hypovitaminosis D
- Vitamin B deficiency: thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate (B9) and cobalamin

Dementia with toxic etiology:
- Alcohol Dementia
- Based on exogenous intoxications: organic solvents, heavy metals, other addictive substances
- Pharmacogenic dementia

Post-traumatic dementia

Dementia in cardiopulmonary and hematological diseases:
- Chronic obstructive pulmonary disease
- Heart failure
- Severe anemia

Dementia in normotense hydrocephalus

Dementia with cancer or neoplasm etiology

Dementia in colagenoses
Classifications of dementias

- irreversible
- reversible
  - identifiable etiology and appropriate treatment

- if the diagnosis of dementia is certain
  - we anticipate a transitory disorder
  - there is no consciousness disorder (then it would be a delirium)
    - organic psychosyndrome
    - mild cognitive disorder
The proportion of dementia types

- Alzheimer: 60%
- Vascular D: 5%
- Mixed AD + VaD: 10%
- Lewy Body D: 3%
- Mixed AD + LBD: 12%
- Frontotemporal: 5%
- Other (mainly secondary): 5%

podľa Králová, 2017
Dementia in Alzheimer disease
F00.0 (G30.0†)

- with early onset
- with late onset
Neuropathological changes in AD

Control

AD

Histopathological finding – the criterion for definitive diagnosis

AP = amyloid plaques
NFT = neurofibrillary tangles

Grossberg, St Louis University, USA
Cortical thickness
Amyloid $\beta$
split by secretases

A$\beta$42 – accumulation and formation of amyloid plaques

tau - tangles

Selkoe a Hardy, 2016
Tau (τ) protein imaging

Maruyma et al., 2013
Genetic risk factor

- **Apolipoprotein E4 (ApoE4)**
  - risk factor for dementia
    - in homozygotes 51% for women 60% chance for men
    - 23% and 30% for carriers of one ApoE4 gene

- higher accumulation of amyloid
  - new findings – also the accumulation of tau protein
    - ApoE3 - common
    - ApoE2 - probable Protective
Vascular dementia

- brain infarcts – microinfarcts
- MID – Multi Infarct Demencia
- **CADASIL**
  - Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts
  - mutation of NOTCH3 gene on 19th chromosome

- risks – Hachinski score
  - acute onset, deterioration in steps, hypertension, cerebrovascular accidents ....

- characteristics
  - memory failure is preceded by a failure of judgment and understanding
  - relatively hypertrophy of long-term memory
  - depression is common
  - visuo-motor abnormalities
Lewy bodies

- α-synuclein = synucleinopathies

LBD = Lewy Body Dementia
- cognitive changes - but do memory failure not necessarily dominates
  - attention, executive ff.
- variations of intensity (difference to AD)
- movement disorders
- REM sleep disorders - RBD - REM Behavior Disorders
- visual hallucinations - detailed - people, animals
- very bad reactivity to antipsychotics (EPS)

Parkinson's disease = substantia nigra
LBD - limbic structures and neocortex

https://www.nia.nih.gov/health/what-lewy-body-dementia
https://commons.wikimedia.org/wiki/File:Lewy_neurites_alpha_synuclein.jpg
Frontotemporal dementia
FTLD – Fronto Temporal Lobar Degeneration

taufaties (Pick disease)
tau-negative forms – ubiquitin positive, protein TDP-43
Variants of FTD

(more recent classification exists)

- **behavioral variant (bvFTD)**
  - early onset
  - change of personality and behavior disturbances dominate
    - e.g. inappropriate sexual behavior

- **language variants**
  - semantic dementia (SD)
  - progressive non-fluent aphasia (PNFA)
    - disturbance of language dominates
Course characteristics of dementias

stationary - eg. posttraumatic D

Down's syndrome mental retardation → dementia

APP coded on 21st chromosome

Alzheimer continuously progressing

confusion, neurological symptoms

vascular
Assessment of severity

- by functionality
  - mild
    - problem in more complicated tasks - new phone, finding the right transport link, financial operations, but the person is not reliant on helping others
  - moderate
    - requires some help – e.g., household maintenance, preparation of meals, doctor visits, dosing of medicines
  - severe
    - depend on day-to-day care

- evaluation by scores of scales measuring cognitive deficits
MMSE
Mini Mental State Examination

- 11 items
- administration in 5 - 10 minutes
  - by physician, nurse, even layman
- only assess cognitive (not behavioral) aspects

- two parts
  - verbal answers to questions about orientation, memory, and attention (maximum score 21)
    - evaluate the ability to name things, make only assess cognitive aspects of psychic functions
  - written and verbal instructions
    - spontaneously write a sentence and copy a complex polygon (maximum score 9)

Folstein et al., 1975
Clock test

Normal
Score 10

Mild Cognitive Impairment
(Numbers error and placement of hands)
Score 8

Moderate Cognitive Impairment
Score 4

Severe Cognitive Impairment
Score 2
Montreal Cognitive Assessment, MoCA
Treatment
Treatment

- Non-pharmacological
  - orientation
  - food
  - cognitive functions training
  - social activities
  - physical activity

- treatment of somatic diseases
- correction of sensory deficits
Cholinergic function

Presynaptic neuron

Acetyl CoA + Choline → ChAT

↓ activity

choline

BuChE

Postsynaptic neuron

Cholinergic receptor

AChE

↓ activity

loss

AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; ChAT = choline acetyltransferase; CoA = coenzyme A

Podl'a Adem, 1992
Inhibitors of acetylcholinesterase:

- donepezil
- rivastigmine
- galantamine
memantine


obrázok: http://www.chemistry.emory.edu/justice/chem190j/EAAreceptors.htm
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<th>Group</th>
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<tr>
<td>Cognitives</td>
<td>acetylcholinesterase inhibitors</td>
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<td>antagonists NMDA receptors</td>
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Králová M. In: Pečenák, Kořinková, Psychofarmakológia, 2016
In the development

- monoclonal antibodies
- vaccines
  - against amyloid
  - against tau
Long-term effects of Aβ_{42} immunisation in Alzheimer’s disease: follow-up of a randomised, placebo-controlled phase I trial

Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial.

Novak P¹, Schmidt R², Kontsekova E³, Zilka N³, Kovacech B³, Skrabana R³, Vince-Kazmerova Z³, Katina S³, Fialova L³, Fricina M³, Parrak V³, Dal-Bianco P⁴, Brunner M⁵, Staffen W⁶, Rainer M⁹, Ondrus M⁹, Ropele S⁹, Smisek M⁹, Sivak R⁹, Winblad B⁹, Novak M². 

targeted to specific part of phosphorylated τ
Course of pathological changes – when to start treatment?

Selkoe & Hardy, 2016
The end