



PARKINSONOVA DEMENCA (PDD)

Moderator: Nina Zupančič Križnar, spec. nevrolog

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Sabina Horvat

PARKINSONOVA DEMENCA

- Subkortikalna demenca (sinukleinopatija), ki se pojavi v 40–70 % PD med potekom bolezni (incidenca 4–6x↑ kot zdravi)
- PDD in DLB imata zgodnje in znatne motnje v vidno-prostorskih funkcijah.
- Histopatološko pri PDD in DLB najdemo Lewyjeva telesca, plake in vaskularne spremembe, amiloid pogosteje pri DLB
- Kriteriji za PDD in sindrom demence (vsaj 2 kognitivni domeni z upadom nivoja funkcioniranja in povzroči upad v socialnem in poklicnem funkcioniranju, deficite kot flukturirajoča pozornost, eksekutivna disfunkcija, prosti priklic in vidno-prostorska funkcija).
- KPSS je relativno neobčutljiv za PDD in DLB, občutljiv MoCA test



I. Core features
Diagnosis of PD +
Dementia syndrome

+

II. Associated clinical features
Impairment of at least two
of four cognitive domains
(May be supported by behavioural symptoms)

PDD diagnosis

**III. Presence of features which
make diagnosis uncertain**

- Co-existence of any abnormality that could itself cause cognitive impairment, but not cause dementia
- Unknown time interval between onset of motor and cognitive symptoms

**IV. Presence of features which
make diagnosis impossible**

Cognitive and behavioural symptoms
presenting as a result of other
conditions, for example:

- Acute confusion due to systemic diseases/ abnormalities or drug intoxication
- Major depression according to DSM IV
- Features of 'probable vascular dementia' according to NINDS-AIREN

—————▶ Probable

- - - - -▶ Possible

—————| Impossible



KRITERIJI ZA DIAGNOZO PDD

Diagnoza PD po kriterijih Queen Square brain bank

- 1) Parkinsonovi boleznj pridružena demenca (PDD) je po definiciji demenca, ki se razvije vsaj 1 leto po diagnozi PD (drugače demenca z Lewijevimi telesci (DLB))
- 2) PD in globalni upad kognicije (KPSS <26 – neobčutljivost!)
- 3) hud kognitivni upad, ki vpliva na dnevne aktivnosti
- 4) deficiti $\geq 2/4$ kognitivnih kortikalnih domen:
 - a) **pozornost** 1 test: odštevanje sedmic (cut off ≥ 2 napaki), naštevanje mesecev v letu od zadaj naprej (cut off izpusti ≥ 2 meseca, nepravilni vrstni red mesecev, ne dokonča v 90s) + spomin
 - b) **eksekutivne funkcije** 1 test: leksikalna fluentnost v 60 s črka S (kratkotrajni spomin+ sledi katere besede že povedal)



KRITERIJI ZA DIAGNOZO PDD 2

- fluentnost besed → velika senzitivnost za PDD (cut off ≤ 9 besed – eksekutivna disfunkcija); test risanja ure eksekutiva > vidno-prostorske funkcije (cut off nezmožnost pravilne postavitve števil in/ali kazalcev)
- c) **vidno-prostorske funkcije**: prerisovanje 2 stikajočih pentagramov



- č) motnje **spomina**: odloženi priklic 3 besed (PDD moten priklic “prostih” besed epizodičnega spomina; cut off ≥ 1 beseda zgrešena)
- odsotnost depresije, delirija ali drugih abnormalnosti, ki bi lahko prikrile diagnozo
- Podporni kriteriji: ≥ 1 od sledečih: apatija, depresija ali anksioznost, halucinacije, deluzije, prekomerno spanje čez dan



TABLE 1. Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
 - Impairment in more than one cognitive domain
 - Representing a decline from premorbid level
 - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
 - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
 - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
 - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
 - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
 - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
 - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
 - Changes in personality and mood including depressive features and anxiety
 - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
 - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
 - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
 - a. Systemic diseases or abnormalities
 - b. Drug intoxication
- Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

TABLE 2. Criteria for the diagnosis of probable and possible PD-D

Probable PD-D

- A. Core features: Both must be present
- B. Associated clinical features:
 - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
 - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis
- C. None of the group III features present
- D. None of the group IV features present

Possible PD-D

- A. Core features: Both must be present
- B. Associated clinical features:
 - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
 - Behavioral symptoms may or may not be present

OR

- C. One or more of the group III features present
- D. None of the group IV features present

TABLE 1. Algorithm for diagnosing PD-D at Level 1

1	A diagnosis of Parkinson's disease based on the Queen's Square Brain Bank criteria for PD ²
2	PD developed prior to the onset of dementia
3	MMSE ³ below 26
4	Cognitive deficits severe enough to impact daily living (Caregiver interview or Pill Questionnaire)
5	Impairment in at least two of the following tests: Months reversed ⁹ or Seven backward ³ Lexical fluency ¹⁰ or Clock drawing ¹⁴ MMSE Pentagons ³ 3-Word recall ³

The presence of one of the following behavioral symptoms: apathy or depressed mood or delusions¹⁶ or excessive daytime sleepiness may support the diagnosis of probable PD-D.
The presence of major depression or delirium or any other abnormality which may by itself cause significant cognitive impairment makes the diagnosis uncertain.

TABLE 2. Diagnostic rating sheet for probable PD-D, recommended by the Movement Disorder Task Force

	YES	NO
1. Parkinson's disease	<input type="checkbox"/>	<input type="checkbox"/>
2. Parkinson's disease developed before dementia	<input type="checkbox"/>	<input type="checkbox"/>
3. MMSE <26	<input type="checkbox"/>	<input type="checkbox"/>
4. Dementia has Impact on ADLs	<input type="checkbox"/>	<input type="checkbox"/>
5. Impaired cognition (For Yes, at least of 2 of 4 tests below are abnormal)	<input type="checkbox"/>	<input type="checkbox"/>
Mark which Tests are abnormal		
<input type="checkbox"/> Months reversed or Sevens backwards		
<input type="checkbox"/> Lexical fluency or clock drawing		
<input type="checkbox"/> MMSE pentagons		
<input type="checkbox"/> 3-word recall		
6. Absence of Major Depression	<input type="checkbox"/>	<input type="checkbox"/>
7. Absence of delirium	<input type="checkbox"/>	<input type="checkbox"/>
8. Absence of other abnormalities that obscure diagnosis	<input type="checkbox"/>	<input type="checkbox"/>
Probable PD-D (items 1-8 must all be YES)	<input type="checkbox"/>	<input type="checkbox"/>



DEJAVNIKI TVEGANJA ZA NASTANEK DEMENCE

- Dejavniki tveganja: višja starost, težja motorična prizadetost PD (rigidnost, posturalna nestabilnost, motnje hoje), blag kognitivni upad ob diagnozi PD, vidne halucinacije povzročene s terapijo
- Vaskularni dejavniki tveganja
- Pri PD izključi delirij, iatrogene učinke antiholinergikov, dopaminergičnih zdravil, BZD ali drugih zdravil
- Izključi ozdravljive vzroke demence ali zmedenosti: infekcija, dehidracija, pomanjkanje vitaminov, endokrinološke motnje, depresija (GDS – geriatric depression scale; cut off >4)



STAROST

Parkinson's disease



Dementia

Parkinson's disease with dementia (PDD)



Dementia

Preclinical

Age (years)

55

60

65

70

75

80



KOGNITIVNI IN NEVROPSIHIATRIČNI PROFIL

- Počasen začetek in potek
- Pozornost: je motena pri PDD in lahko fluktuirata, bolj kot pri AD
- Spomin: motnje verbalnega in vizualnega spomina, vendar manj kot pri AD; prizadetost priklic > prepoznavna pri blagi do srednji PDD (namig izboljša priklic)
- Eksekutivne funkcije: bolj prizadete kot pri AD, blaga anomija in motena verbalna fluentnost ; več eksekutivne disfunkcije in več pogostejših psihoz je pri DLB kot PDD
- Konstrukcije in praksije: vidno-prostorske konstrukcije so prizadete mnogo bolj kot AD
- Jezik: manj težav pri kortikalni funkciji jezika kot AD
- Vidne halucinacije



TESTI

TABLE 3. *Summary of Tests at Level II testing for PD-D*

Global efficiency	Mattis DRS ²⁰
Executive functions	
Working memory	Digit span ²⁵ Spatial span (CANTAB) ²⁹ Digit ordering test ³²
Conceptualization	Similarities (WAIS-III) ³⁴ Wisconsin CST ³⁶
Set activation	Verbal fluency (C, F, L) ^{10,21}
Set shifting	TMT ⁴⁰
Set maintenance	Stroop test ^{21,42} Odd man out test ⁴³ Prehension behavior ⁴⁴
Behavioral control	
Memory	RAVLT ^{53,55} Free and cued recall test ^{15,54}
Instrumental functions	
Language	Boston naming test ⁵⁷
Visuo-constructive	Copy of the clock ^{14,59}
Visuo-spatial	Benton line orientation test ⁶⁰ Cube analysis (VOSP) ⁶¹
Visuo-perceptive	Benton face recognition test ⁶³ Fragmented letters (VOSP) ^{61,64}
Neuropsychiatric functions	
Apathy	Apathy scale ⁴⁷
Depression	MADRS ⁶⁶ Hamilton ^{19,66} Beck depression inventory ⁶⁷ GDS-15 ⁶⁸
Visual hallucination	PPQ ⁶⁹
Psychosis	NPI ⁵⁰



VEDENJSKI IN NEVROPSIHIATRIČNI SIMPTOMI

- Vsaj 1 psihiatrični simptom najdemo pri 83% PDD
- halucinacije in deluzije: če še ni dementen → halucinacije glavni “prediktor” demence (lahko posledica terapije z dopaminergičnimi zdravili)
- Vidne halucinacije so indikator hitre kognitivne deterioracije in začetka demence pri PD. Ločijo DLB in PDD od AD.
- Apatija: značilna za FTD in PSP, tudi DLB in AD, manj PDD



VEDENJSKI IN NEVROPSIHIATRIČNI SIMPTOMI 2

- Nevropsihiatrični simptomi so pogosti pri PDD, skoraj vsi bolniki imajo spremembe osebnosti (socialni umik in apatija) Najpogostejši nevropsihiatrični simptomi so depresija, halucinacije (vidne 2x↑), nato apatija pri blažjih stadijih medtem ko so deluzije (več kot pri PD a manj kot pri DLB) pogostejše pri težjih motorični in kognitivni disfunkciji, anksioznost, tudi psihoza, čezmerna dnevna zaspanost.
- Pogosto REM sleep behavior disorder



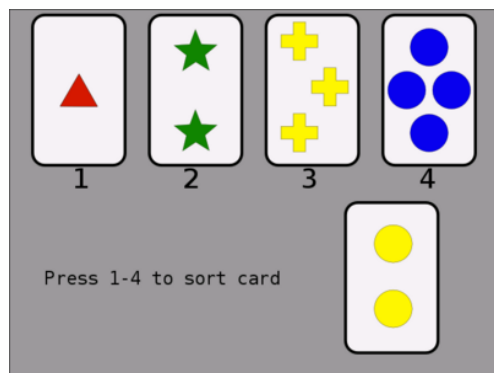
SLIKOVNE PREISKAVE

- FDG-PET: ↓Glc metabolizem inferiorno parietalno in okcipitalno in temporalno
- Prisotna je bila hipoperfuzija v lateralnih delih parieto-okcipitalnega korteksa pri DLB in PDD glede na AD (dobra korelacija).
- Parietalne regije so vpletene v vidno-prostorsko procesiranje, ki je moteno pri PD, PDD in DLB.
- DAT scan: Pri DLB in PDD je signifikantna redukcija privzema vezalca za DAT bilateralno v kaudatusu in putamnu. Ne moremo ločiti med DLB in PDD glede na nivo vezave dopaminskega transporterja.
- Bolniki z vidnimi halucinacijami imajo frontalno hipermetabolizem in orbitofrontalno atrofijo, ki korelira z deficiti vidnega spomina.

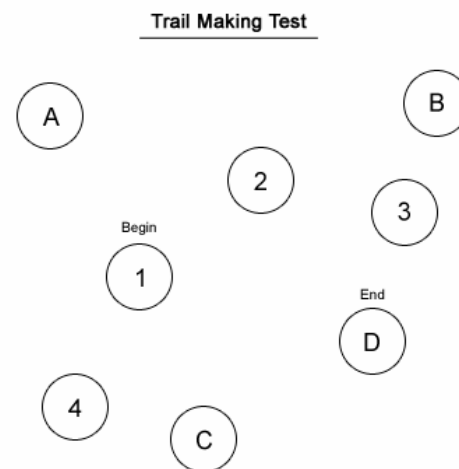


NEVROPSIHOLOŠKO TESTIRANJE

- Eksekutivne funkcije:
Wisconsin card sorting test
(pozornost in mentalna rigidnost), verbalna fluentnost (semantična, črka)



- Eksekutivne funkcije:
Stroop test, Trail making test



NEVROPSIHOLOŠKO TESTIRANJE 2

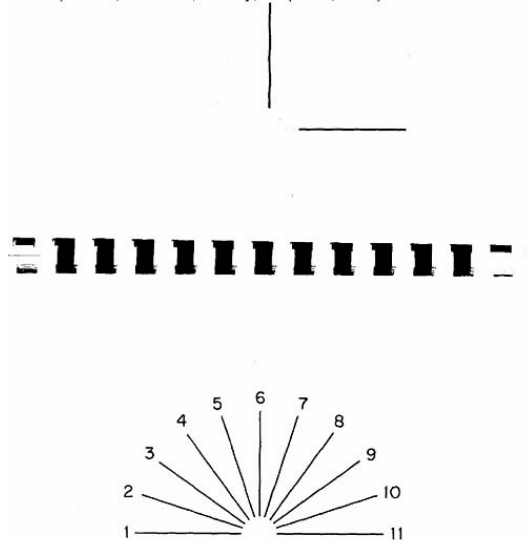
- Eksekutivna disfunkcija – procesi, ki so potrebni za realizacijo kompleksnih kognitivnih nalog, ki potrebujejo selekcijo informacij za procesiranje, najti pravilo, spremeniti način mišljenja, rešiti večstopenjski problem, se upreti kognitivnim interferencam, deliti pozornost in aktivno priklicati informacije
- Povezava z delovnim spominom



NEVROPSIHOLOŠKO TESTIRANJE 3

- • Delovni spomin: digit span
- • Spomin: prosti in priklic z namigom, avditorno verbalno učenje
- • Vidno-prostorske sposobnosti: test risanja ure, Benton line orientation, prepoznava obrazov, fragmentirane črke

An example of an item from the Judgement of Line Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983)



ZDRAVLJENJE

- **Rivastigmin** izboljša kognitivno funkcijo in vedenjske simptomie pri DLB in pri PDD ter ne pride do poslabšanja motoričnih simptomov (Aarsland et al, 2004).
- Rivastigmin stranski učinki na GIT (nausea, bruhanje) in poslabšanje tremorja ~ 10%.
- **Rivastigmin** je registriran za zdravljenje PDD.
- **Memantin** ne poslabša motorike pri PDD ali DLB. Najpogostejši stranski učinek je somnolenca. (terapija za blago do srednje težko DLB).

TABLE 2

MEDICATIONS FOR PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

<i>Generic Name</i>	<i>Trade Name</i>	<i>Initial Dose</i>	<i>Final Dose</i>	<i>Precautions</i>	<i>Advantages</i>
Rivastigmine	Exelon patch	4.6 mg	9.5 mg	Transient, initial nausea vomiting; titrated up at week 4; abrupt withdrawal leads to abrupt decline; patch must be rotated to different areas	Transdermal patch applied once daily; FDA approved for Parkinson's dementia
Donepezil	Aricept	5 mg	10 mg	Transient, initial nausea vomiting; titrated up at week 4; abrupt withdrawal leads to abrupt decline	Oral dose taken QD

FDA=Food and Drug Administration.

Kennedy GJ. *Primary Psychiatry*. Vol 16, No 4. 2009.