2023-11-23 Lund Sv Park Akad

Prodromalfasen – Parkinsons sjukdom

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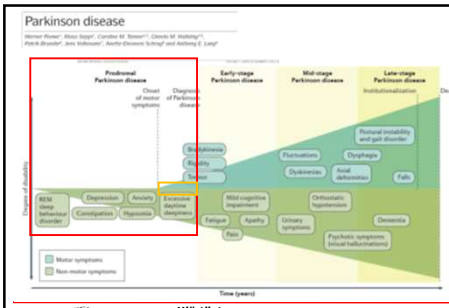

Prodromal fasen

Perioden före en klinisk diagnos av Parkinsons sjukdom

Kan-men behöver inte föregås av

Intermittenta motoriska
Icke motoriska symtom

Möjliga mekanismer
Vid dopaminbrist har kvarvarande nervceller utvecklat kompensationer:
–TH, tyrosinhydrokinas (x 3- 5)
- Dopaminomsättning (x 5 – 7)
  - Mer fria radikaler/oxidation

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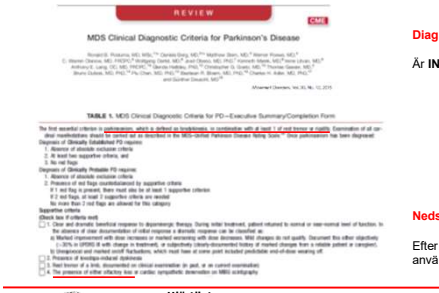

Diagnoskriterier för PD

Är **INTE** uppfyllda i prodromal fasen

Nedsatt luktsinne

Efter CoVID pandemin inte ett användbart symtom eller kriterium

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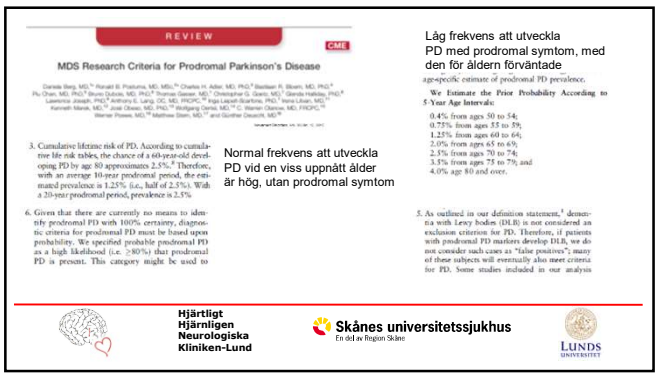

REVIEW

CME

MDS Research Criteria for Prodromal Parkinson's Disease

Låg frekvens att utveckla PD med prodromal symtom, med den för åldern förväntade

Normal frekvens att utveckla PD vid en viss uppnått ålder är hög, utan prodromal symtom

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4

Revidering och ny upplaga 2019

REVIEW

Update of the MDS Research Criteria for Prodromal Parkinson's Disease

A Web-based Medical Calculator for Prodromal Risk in Parkinsonism

Authors: Sebastian Heinzel PhD, Daniela Berg MD, Thomas M. Gasser MD, Honglei Chen MD, Chun Yao MSc, Ronald B. Postuma MD, MSc
Architectured by: Chun Yao

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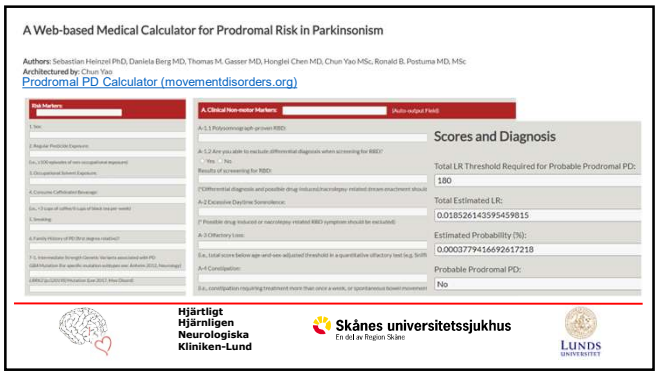
5



A Web-based Medical Calculator for Prodromal Risk in Parkinsonism

Authors: Sebastian Heinzel PhD, Daniela Berg MD, Thomas M. Gasser MD, Honglei Chen MD, Chun Yao MSc, Ronald B. Postuma MD, MSc
Architectured by: Chun Yao
Prodromal PD Calculator (movementdisorders.org)

Scores and Diagnosis

Total LR Threshold Required for Probable Prodromal PD: 180

Total Estimated LR: 0.018526143595459815

Estimated Probability (%): 0.0003779416692617218

Probable Prodromal PD: No

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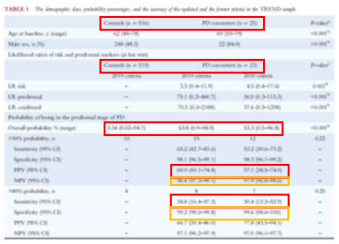
6

Comparing the Two Prodromal Parkinson's Disease Research Criteria—Lessons for Future Studies

Rezzak Yilmaz, MD,[1*] Ulrike Suenkel, MD,[2] The TREND Study Team, Ronald B. Postuma, MD, MSc,[3] Sebastian Monzel, PhD,[2] and Daniela Berg, MD[1,2]

Movement Disorders, Vol. 36, No. 7, 2021



Ingen avgörande förbättring av klinimetriska data

Av 516 prodromal fas patienter
-> konvertering till PD under 3 år
23 - 25 st

Mycket lågt sensitivitet för sannolik prodromal fas (80% nivå) – 1/3
Prediktivt värde 67% (2/3)

7

Tillägg av genetisk riskfaktor

A Remote Longitudinal Observational Study of Individuals at Genetic Risk for Parkinson Disease

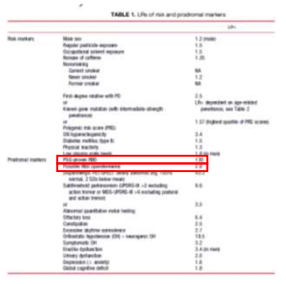
Baseline Results

277 *LRRK2* G2019S carriers

24 prodromal PD
9 probable prodromal PD
20 symtomatiska – flest äldre

Gen-prenetrans / ålder

8



Likelihood rate för fenotypisk konversion
För REM sömns sjuka (RBD)

PSG påvisad RBD 130

pRBD (anamnes/frågeformulär)
2,8

Data of 541 participants were analyzed (Table 1). Within 10 years, 2.5 participants converted to PD. As 6 were diagnosed at baseline, longitudinal data were available for 17 converters.

The positive predictive value was low with wide confidence intervals for both criteria. The specificity and negative predictive values were very high. These results are similar to the findings of another cohort with 10 years' follow-up[5] and indicate that even in an enriched cohort at risk for neurodegenerative diseases followed a decade, the inclusion of markers more specific to PD is necessary to detect individuals in their prodromal stage. Thus,

based on their high likelihood ratios, polysomnography-confirmed RBD or DATScan is needed to increase the sensitivity of the criteria, at least until surrogate biomarkers for the prodromal stage are broadly available.[5,6]

9

American Academy of Sleep Medicine.
International Classification of Sleep Disorders. 3rd ed. 2014

REM sömnsbeteende störning (RBD)

(1) Upprepade episoder av
Utlevda drömmar – beteende / vokalisering under REM sömn
- **dokumenterade med polysomnografi**
  - om inte dokumenterad: förmodad utlevd dröm

(2) Upprepade episode av **REM sömn utan atoni** enligt **polysomnografi**
- Utan dokumenterad REM sömnsfas utan atoni
  - Provisorisk REM sömnsbeteende störnings diagnos, pRBD
  - Högfrekvent tillstånd 5.65 (95% CI = 4.29–7.18%) av befolkning

Utlevda drömmar (utan atoni) narkolepsi
läkemedel – SSRI / SNRI

Utlevda drömmar (med atoni i REM) narkolepsi
läkemedel – SSRI / SNRI } **RBD**

Tal, rop och skrik under natten är inte tillräckligt för RBD diagnos

Differential diagnostik till RBD

Icke REM sömn parasomni (sömngång)

Obstruktiv sömn apné

PMLS – period limb movements during sleep (vanligt vid RLS)

Narkolepsi

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10

The REM Sleep Behavior Disorder Screening Questionnaire—A New Diagnostic Instrument

Karin Stiasny-Kolster, MD,[1] Geert Mayer, MD,[1] Sylvia Schäfer, MD,[1] Jens Carsten Möller, MD,[1] Monika Heinzel-Gutenbrunner, PhD,[1] and Wolfgang H. Oertel, MD[1]

5 (yes) p – misstänkt RBD
Utredes vidare med PSG för definitiv diagnos

TABLE 1. *RBD Screening Questionnaire*

	Question
English	
1.	I sometimes have very vivid dreams.
2.	My dreams frequently have an aggressive or action-packed content.
3.	The dream contents mostly match my nocturnal behaviour.
4.	I know that my arms or legs move when I sleep.
5.	It thereby happened that I (almost) hurt my bed partner or myself.
6.	I have or had the following phenomena during my dreams:
6.1	speaking, shouting, swearing, laughing loudly
6.2	sudden limb movements, "fights"
6.3	gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes,
	falls off the bed
6.4	things that fell down around the bed, e.g., bedside lamp, book, glasses
7.	It happens that my movements awake me.
8.	After awakening I mostly remember the content of my dreams well.
9.	My sleep is frequently disturbed.
10.	I have/had a disease of the nervous system (e.g., stroke, head trauma, parkinsonism, RLS, narcolepsy, depression, epilepsy, inflammatory disease of the brain), which?

TABLE 3. *Sensitivity and specificity of single RBDSQ items*

RBDSQ item	Sensitivity (%)	Specificity (%)	Item-test correlation
1	94.4	47.1	0.636 ($P < 0.0005$)
2	83.0	71.9	0.730 ($P < 0.0005$)
3	80.0	75.2	0.732 ($P < 0.0005$)
4	88.7	57.4	0.719 ($P < 0.0005$)
5	68.5	85.3	0.693 ($P < 0.0005$)
6.1	90.7	62.5	0.752 ($P < 0.0005$)
6.2	82.7	59.2	0.739 ($P < 0.0005$)
6.3	56.0	91.1	0.635 ($P < 0.0005$)
6.4	49.1	88.4	0.627 ($P < 0.0005$)
7	71.7	49.3	0.527 ($P < 0.0005$)
8	74.1	42.2	0.366 ($P < 0.0005$)
9	81.1	23.9	0.343 ($P < 0.0005$)
10	56.6	56.3	0.367 ($P < 0.0005$)

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11

Original Article

Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK)

S.X. Li[a], Y.K. Wing[a,*], S.P. Lam[a], J. Zhang[a], M.W.M. Yu[a], C.K.W. Ho[a], J. Tsoh[a], V. Mok[b]

Sleep Medicine 11 (2010) 43–48

Symptoms	Lifetime occurrence: I don't remember/ I don't know	No	Yes	Recent 1-year frequency: Did it happen in the recent 1 year?	Once or few times per year	Once or few times per month	1–2 times per week	3 times or above per weeks
1. Did you often have dreams?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
2. Did you often have nightmares?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
3. Did you have dreams with an emotional and sorrowful content?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
4. Did you have dreams with a violent or aggressive content (e.g., fighting with someone)?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
5. Did you have dreams with a frightening and horrifying content (e.g., being chased by ghost)?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
6. Did you have sleep talking?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
7. Did you shout, yell or swear during your sleep?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
8. Did you move your arms or legs in response to your dream contents during sleep?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
9. Have you ever fallen from your bed?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
10. Have you ever hurt yourself or your bed-partner while you were sleeping?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
11. Have you ever attempted to assault your bed-partner or almost hurt yourself while you were sleeping?	□	□	□	□ Yes □ No (Please go to the next question)	□	□	□	□
12. The situations described in 10 or 11 relate to your dream contents?	□	□	□	□ Yes □ No	□			
13. Did the situations described above disturb your sleep?	□	□	□	□ Yes □ No	□			

RBDQ-HK Subscale (factor 2 questions)	Sensitivity (%)/ specificity (%)	PPV	NPV
Overall (0–70)	87.9%/81.3%	82.5%	87.0%

Cut off <18/>19 / 100
Cut off <7/>8 / 70

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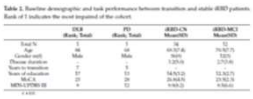
Article

Exploring the Sensitivity of Prodromal Dementia with Lewy Bodies Research Criteria

Joseph R. Phillips [1,2], Elie Matar [1], Kaylena A. Ehgoetz Martens [1,3], Ahmed A. Moustafa [4,5], Glenda M. Halliday [1,6] and Simon J. G. Lewis [1,7]

Brain Sci. 2022, 12, 1594. https://doi.org/10.3390/brainsci12121594

A total of 47 iRBD participants, 6 female, with a mean age of 68.7 (SD = 8.0) years, were recruited from the ForeFront Parkinson's Disease Research Clinic at the Brain and Mind Centre, University of Sydney, where they form part of an ongoing, prospective longitudinal study that typically aims to review patients every 12 months. Unfortunately, the COVID-19



1 / 13 patients who would have satisfied the current guidelines for probable pDLB transitioned to DLB after two years

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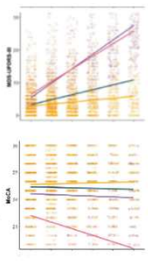
BRAIN

ORIGINAL ARTICLE

Progression of clinical markers in prodromal Parkinson's disease and dementia with Lewy bodies: a multicentre study



>1200 iRBD patienter

3 års konvertering till PD/DLB ca 20%

Kognitiva symtom – tillkommer för DLB endast

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Prodromal symtom som inte har något prediktivt värde:

- nedsatt luktsinne	CoVID	
- förstoppning	(definition: daglig bruka av laxantia varannandags tarmtömning bestående över tid)	
	mkt ospecifikt	Samband finns – retrospektivt av PD patienter hög andel har haft långvarig förstoppning
		Prediktivt värde av dem som har förstoppning mkt lågt
- depression	mkt ospecifikt	Mild/moderat depression – x 6-7 (dopaminbrist ?) Svår depression ingen ökning

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Begränsningar med begreppet ”prodromal fas”- 2ndär parkinsonism

Kända genbärare

Småkärls sjukdomar – diabetes, hypertoni, hyperkolesterolemi, rökning

Tidigare läkemedelsbehandling

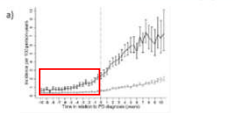
neuroleptika
antikolinergika
narkotika — metamfetamin, amfetamin, MPTP och analoger, MME, Mangan-metkatinon encefalopati

Symtom utan dopaminbrist (SWEDD) annan atypisk DAT/PET scan

16

Incidence of antipsychotic use among community dwellers with and without Parkinson's disease

Satu Lilja, Anna-Maija Tolppanen, Marjaana Koponen, Sirpa Hartikainen, Miia Tiihonen



The difference was mainly explained by the quetiapine use, which was the most commonly initiated antipsychotic among people with PD in our study. In addition to treating psychotic symptoms, quetiapine is used in off-label treatment of insomnia. This off-label use is relatively common in Finland.

Psychotic symptoms may be challenging to recognize as prodromal symptoms of PD since they can occur years before the motor symptoms and thus, they cannot be clinically associated with the diagnosis of PD.

Tidigare läkemedel viktig faktor som inte är fullt kartlagd i prodronal fasen / roll i utveckling

Neuroleptika
Anti-kolinergika

BMJ Journals
Journal of Neurology, Neurosurgery & Psychiatry

Research paper

Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study

The cognitive decline was higher in those who had been taking AA drugs (median decline on MMSE 6.5 points) compared with those who had not taken such drugs

Journal of Neurology, Neurosurgery & Psychiatry 2010; 81 129-129

17

REVIEW

Unexpected (^{123}I)FP-CIT SPECT findings: SWIDD, SWEDD and all DAT

Balestrino Roberta[1,2] · Barone Paolo[3] · Filippi Massimo[4,5,6] · Erro Roberto[3]

SWEDD: Scans Without Evidence of Dopaminergic Deficit
SWIDD: Scans With Ipsilateral Dopaminergic Deficit

A negative DaTSCAN excludes a diagnosis of PD, it does not exclude other atypical parkinsonisms

Patients with a clinical diagnosis of PD

SWEDD
3.6% CALM-PD study
19.6% European FP-CIT study

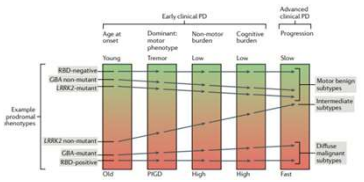
18

Nya begrepp – prodromal subtyper

Prodromal Parkinson disease subtypes — key to understanding heterogeneity

D Berg, P Borghammer, S-M Fereshtehnejad, S Heinzel, J Horsager, E Schaeffer, RB Postuma
Nature Reviews Neurology **volume 17**, pages349–361 (2021)

- Possible subtypes of prodromal PD are
- REM sleep behaviour disorder subtypes
- brain-first and body-first subtypes
- genetic subtypes and
- biological subtypes.

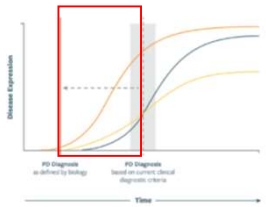


19

Nya begrepp – sjukdomsdefinition

Review

Proposal for a Biologic Staging System of Parkinson's Disease



20

Prodromal fasen av Parkinsons sjukdom

Av intresse endast som forskningsbegrepp (inte färdig studerat / definierat)

Patientgrupper med klinisk relevans – där det finns ngt konkret att följa

Genbärare
PSG verifierad RBD
Asymtomatisk DA brist på PET

21