UNEMEDITSIINI KONVERENTS

II interdistsiplinaarne koostöökonverents

16.10.2020, TALLINN

MEDITSIINI-
KONVERENTSID

medicum
Terve elu!

TALLINNA ÜLIKOOL
Loodus- ja terviseteaduste instituut

IDA-TALLINNA KESKHAIGLA

CONFIDO

Rahututute jalgade sündroom
Parkinsoni tõve prodroom

Prof. Toomas Toomsoo MD, PhD
TLÜ Loodus- ja terviseteaduste instituut neurobioloogia ja neuroloogia külalisprofessor
Ida Tallinna Keskhaigla neuroloogiakeskus
Confido Erameditsiinikeskus

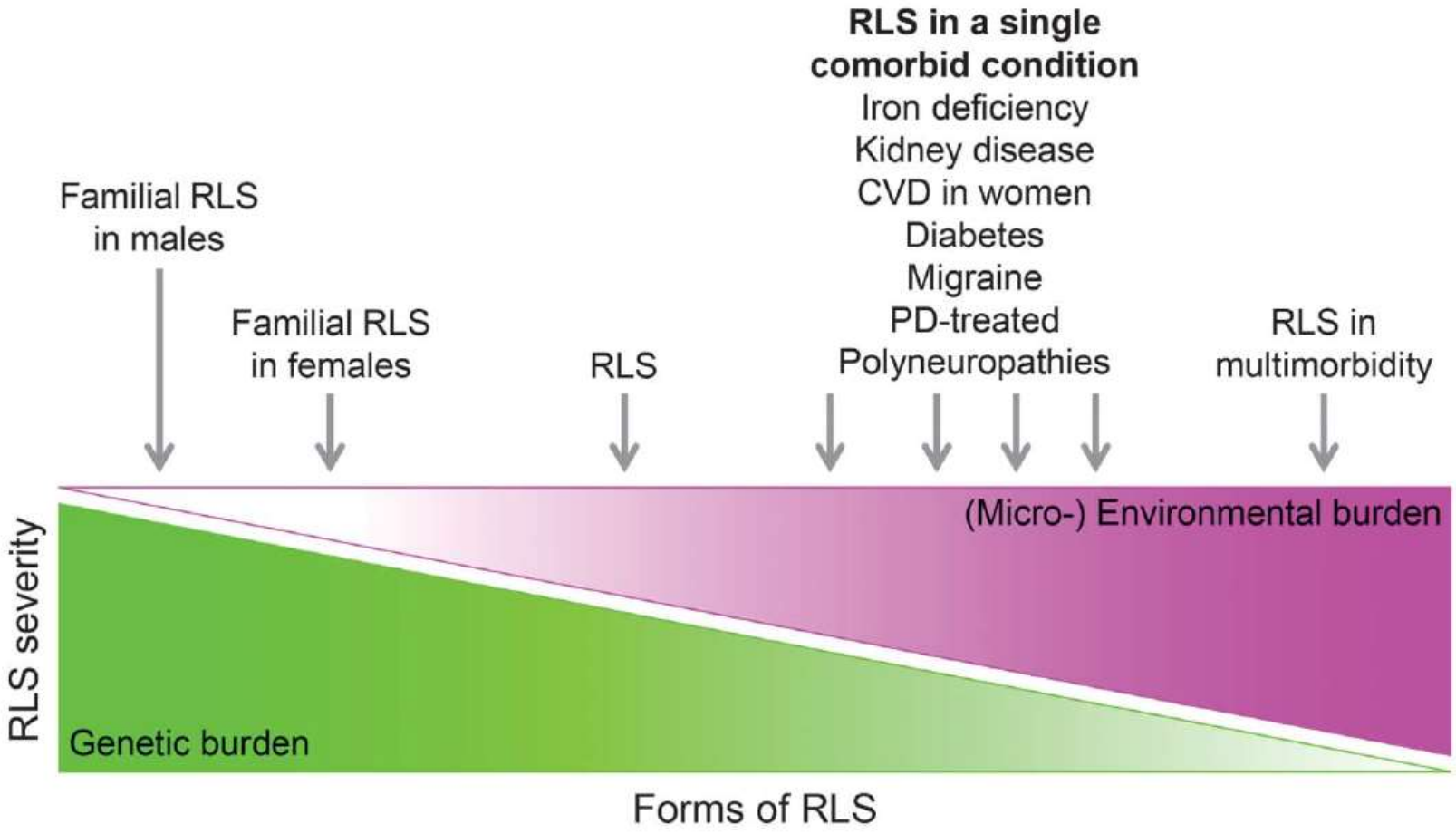
Rahututе jalgade sündroom

RJS esmased diagnoosikriteeriumid 1995
revideeritud kriteeriumid 2003
revideeritud kriteerium 2014

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the Restless Legs Syndrome Diagnosis and Epidemiology Workshop at the National Institutes of Health. Sleep Med 2003;4:101–119.

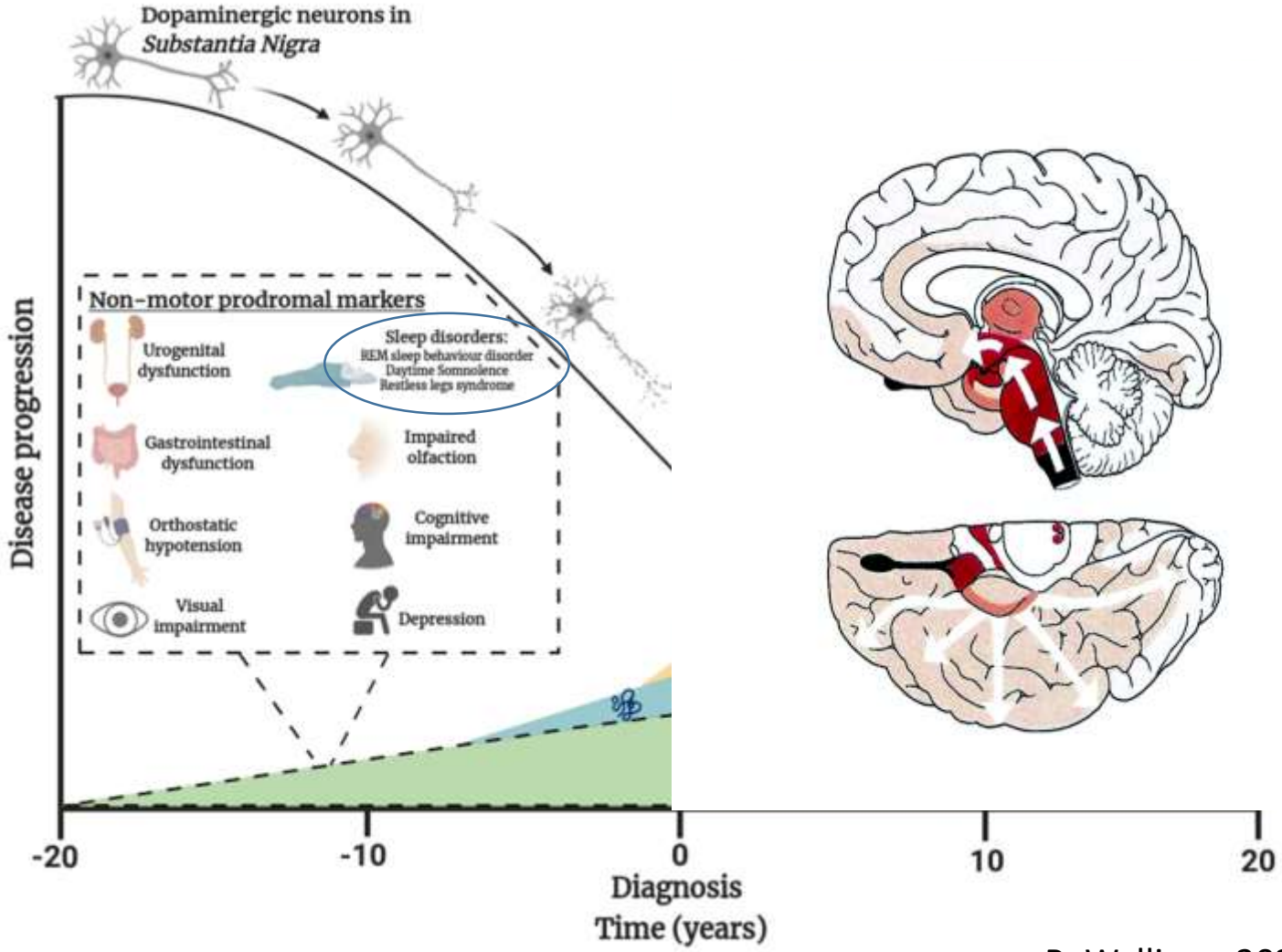
Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria: history, rationale, description, and significance. Sleep Med 2014;15:860–873

Rahututе jalgade komorbiidsus



Trenkwalder, 2016

Parkinsoni tõve prodroom



R. Wallings, 2020

Advances in markers of prodromal Parkinson disease

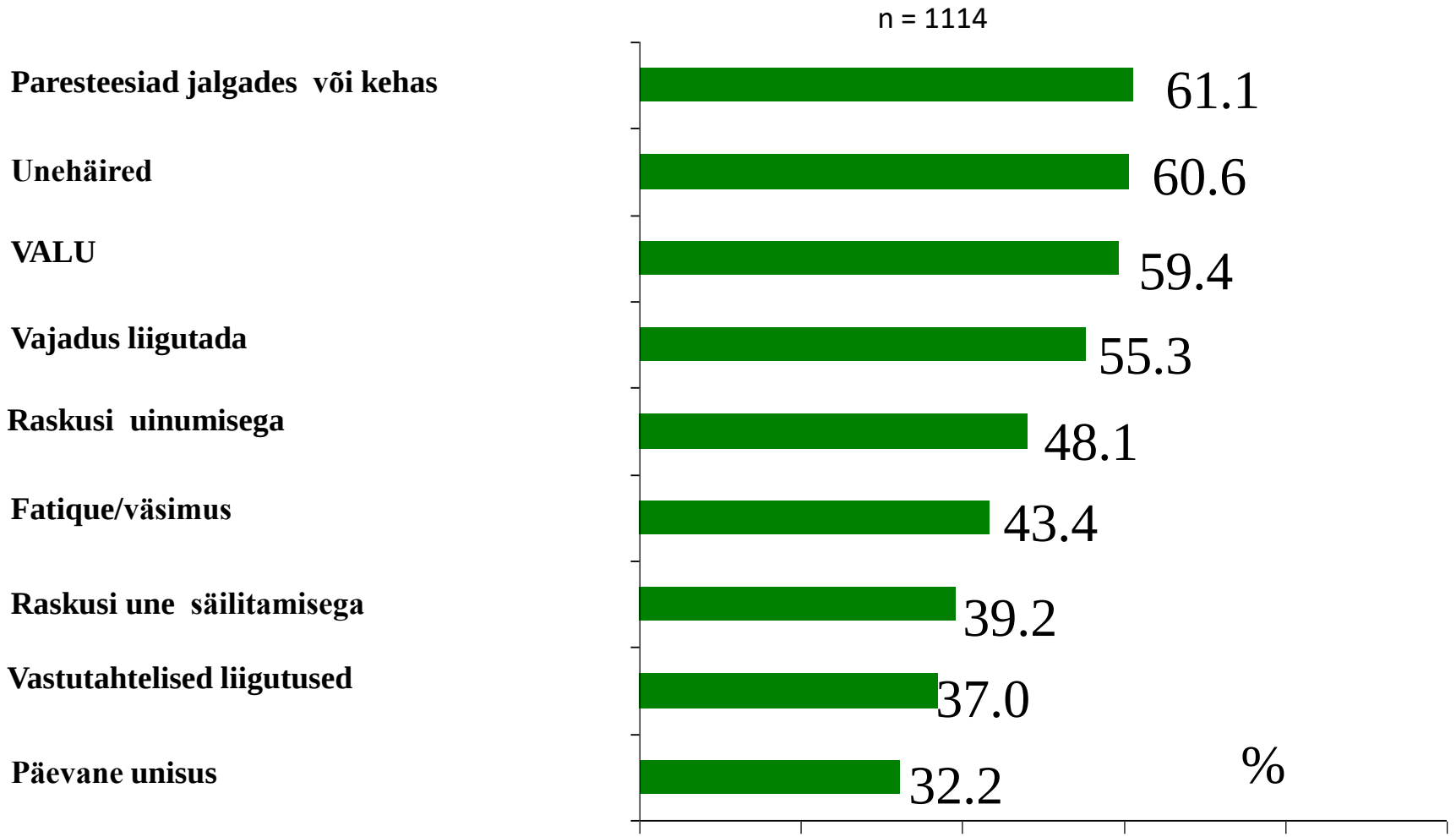
Table 1 | **Properties of identified markers of prodromal PD**

Marker	Level of evidence*	Approximate relative risk	Estimated lead time (years)[‡]	Testing cost[§]	Refs
Olfactory loss	High	5	Not estimated	Low to moderate	20–24,46–50
REM sleep behaviour disorder	High	50	13	Low for screens, high for polysomnogram	32–36
Somnolence	Moderate	1.8	Not estimated	Low	70–74
Restless legs syndrome (late onset)	Low	1.5	Probably <4	Low	85
Constipation	High	2.5	>15	Low	57–62
Orthostatic hypotension	Moderate	2–10 (uncertain)	2–10 years (not directly measured)	Low	61,67
Urinary dysfunction	Low to moderate	2.1	>5 years (uncertain)	Low	60,61
Erectile dysfunction	Low to moderate	1.2 (mild), 3.8 (severe)	5–10 years	Low	61,69
Depression and anxiety	High	1.8	Uncertain, possibly biphasic	Low, but high for follow-up	61,75–80
Colour vision loss	Low	2.5	>3 years (uncertain)	Moderate	49,86
Subtle parkinsonism	Moderate	10	4–5	Moderate to high (expert examination required)	17,43
Quantitative motor testing	Moderate	3–4	5	Moderate	43,44
Substantia nigra hyperechogenicity	Moderate	15	Uncertain, possibly a risk marker	Moderate to high	17,94,100
Dopaminergic PET/SPECT abnormalities	Low (but high plausibility)	20	5	High	18,51,94
PD-related pattern on SPECT/PET	Low	Unknown	Not estimated	High	106
Hippocampal hyperperfusion	Low	Unknown	Not estimated	High	107
Electrocardiogram beat-to-beat variability	Low	2	Up to 20	Low	108,109
α-Synuclein gastrointestinal biopsy	Low	3 (uncertain)	Not estimated	High	112–114

*Markers with prospective evidence of predictive value are included. An entry of 'low' implies a single study, 'moderate' implies more than one high-quality study, and 'high' implies more than four high-quality studies. High-quality means at least a prospective study that assessed the marker before patients developed Parkinson disease, then monitored the patients over time. This definition allowed inclusion of large-scale population health studies if the marker was assessed prospectively. [‡]Lead time refers to the approximate time point before the onset of PD at which the marker deviates from normal values, but not the time at which the marker is reliably abnormal, which cannot be estimated for most markers. [§]For testing cost, 'low' indicates that patients can be screened with a questionnaire that does not require a visit, 'moderate' implies that assessment in person is required but the cost is low, and 'high' implies requirement for extensive or expensive evaluation (cost >$200). All estimates are likely to change as further studies are completed. PD, Parkinson disease; REM, rapid eye movement; SPECT, single-photon emission CT.

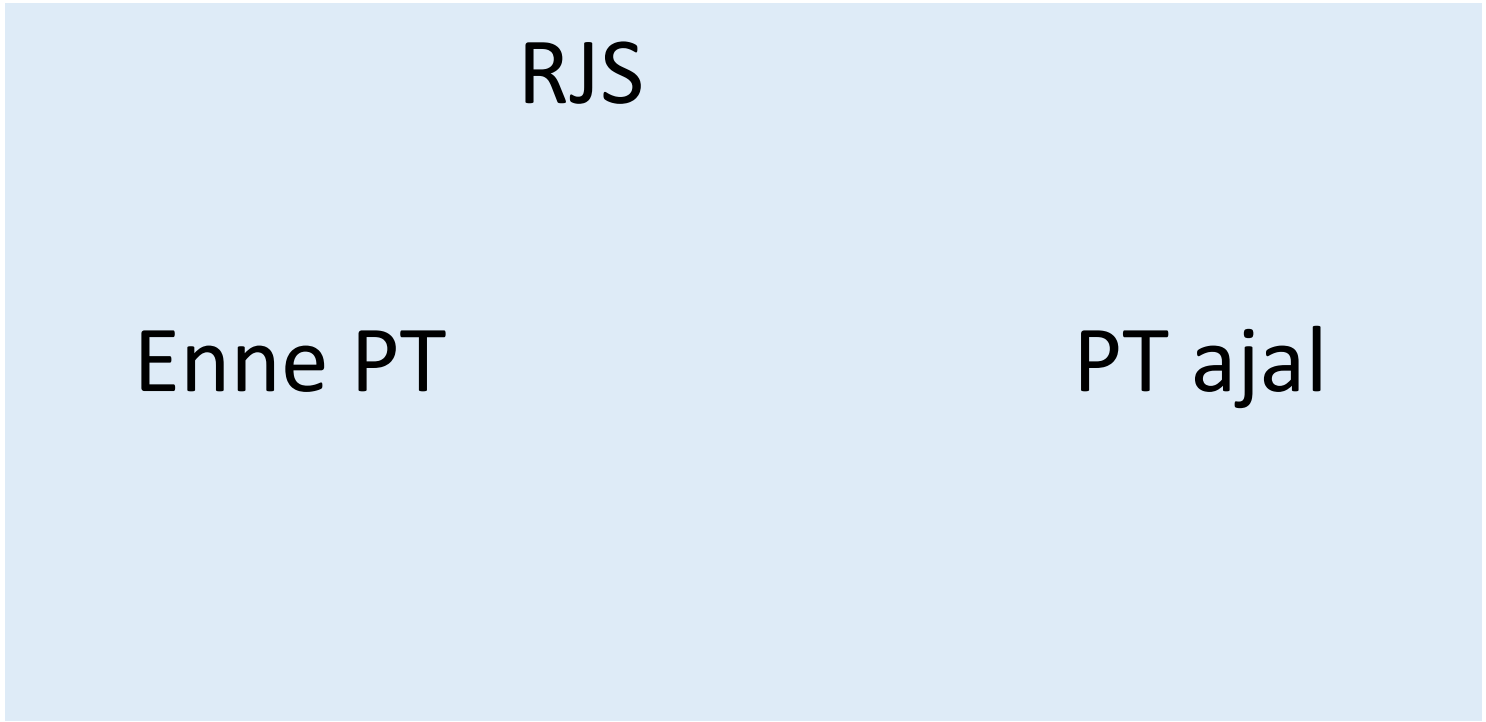
Postuma, Berg 2016, Nature Reviews Neurology

RJS kaebused arstile vs PT mitte- motoorsed sümptomid



Allen et al. Arch Intern Med 2005; 165:1286-1292

Miks me arvame, et RJS on Parkinsoni tõvega seotud ?



Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. Neurology 1976;26:423–429.

RJS kui potentsiaalne PT riskifaktor

Calzetti et al., 2014[e49]	Italy	Prevalence of RLS: 14.15%; incidence rate 47/1,000 cases/person per year (37 per 1,000 case/person per year after excluding secondary RLS); higher incidence in the overall group from 55 to 64 years (70 per 1,000 cases/person per year), and in women aged 65–74 y (106 per 1,000 cases/person per year); there was no significant difference in sex, age at onset, duration, the severity of PD, and levodopa equivalent dose between PDRLS and PDNRLS patients; the median time interval between the onset of PD and RLS symptoms: 25 months (range 9–88 months) and 12.5 months (range 1–79 months) between the onset of dopaminergic therapy and RLS symptoms
Moccia et al., 2016[e50]	Italy	Prevalence of RLS: 4.6% at baseline, 6.5% at 2 years, and 16.3% at 4 years of follow-up; there was no significant difference in sex, age, duration and severity of PD, and levodopa equivalent dose between PDRLS and PDNRLS patients; older age was more likely associated with increased RLS occurrence during follow-up; increased dopaminergic transporter availability of affected caudate and putamen was more likely associated with RLS presence at diagnosis and during follow-up
Marchesi et al., 2016[e51]	Italy	Cumulative incidence of idiopathic RLS during the follow-up period 11.9%; there was no significant difference in sex, age, duration and severity of PD, or levodopa equivalent dose between PDRLS and PDNRLS patients

RJS enne PT
25 kuud varem (9- 88 kuud)

PT : kaasuvad sümptomid

OFF episoodid

Rigiidsus

Düstoonia

Ärevus

Düskineesia

Sisemine treemor

RJS

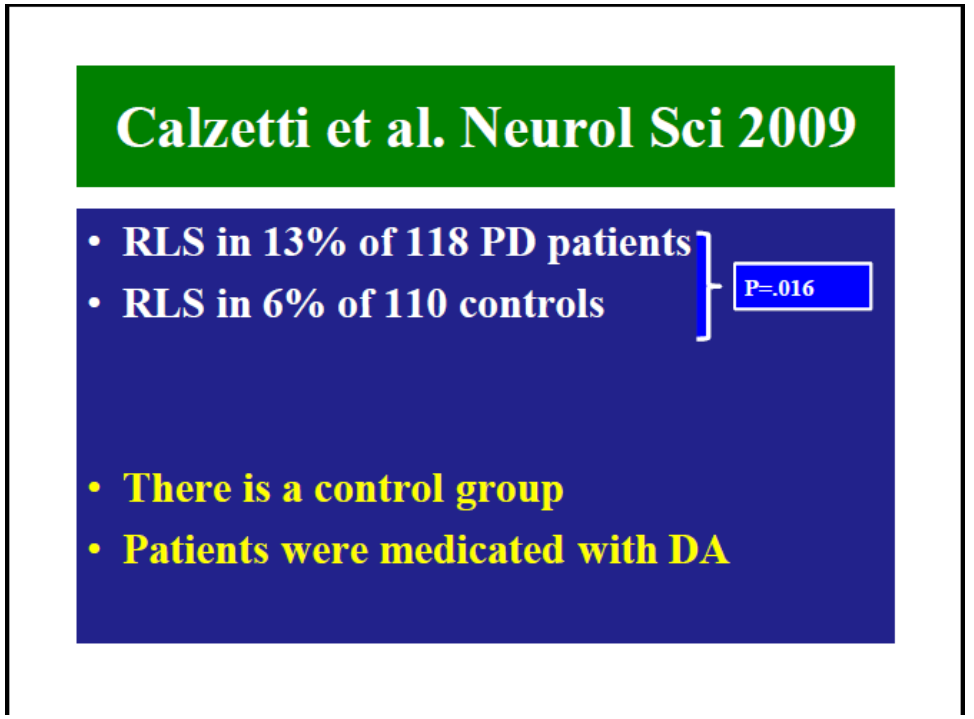
Klaustrofoobia

Tsentraalne valu

Krambid jäsemetes

RJS → PT

PT → RJS



RJS Parkinsoni tõve patsientidel ja mitte- PT patsientidel

VANUS

Üldiselt pole vahet, mis vanusest on jutt

RJS esines enam naistel vanuses 55-64 aastat

VANUS PT tekkel

RJS sama vanadel, kellel PT või kellel mitte

PT KESTUS

Pole oluline võrreldes mitte PT patsientide RJS

Vaid 3 uuringut on näidanud, et RJS võib esineda pikema PT kestuse korral

Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

RJS Parkinsoni tõve patsientidel ja mitte- PT patsientidel

PT RASKUS

Pole vahet kas on raskem PT või mitte või pole üldse PT

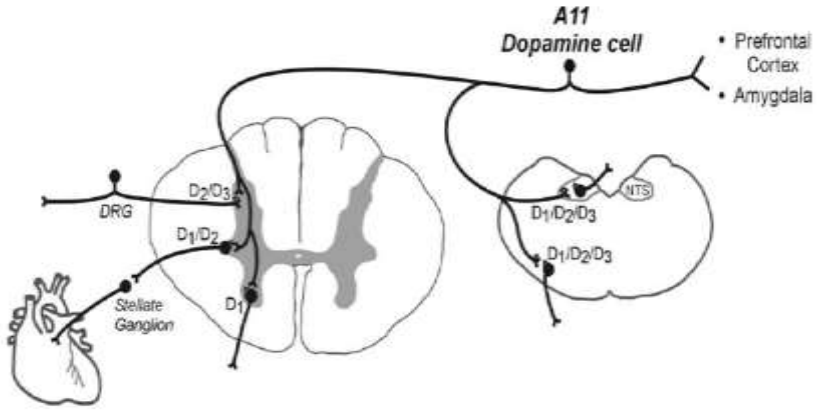
LDED

Pole vahet milline on LD ekvivalentdoos

Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

RJS- patofüsioloogia

- Keskaju perihüpotalaamiline dopaminergilise süsteemi alafunktsioon (A11 D neuronid)
- Seljaaju sensomotoorne süsteem (Thomas, Watson, 2008)
- Raua a/v häirumine

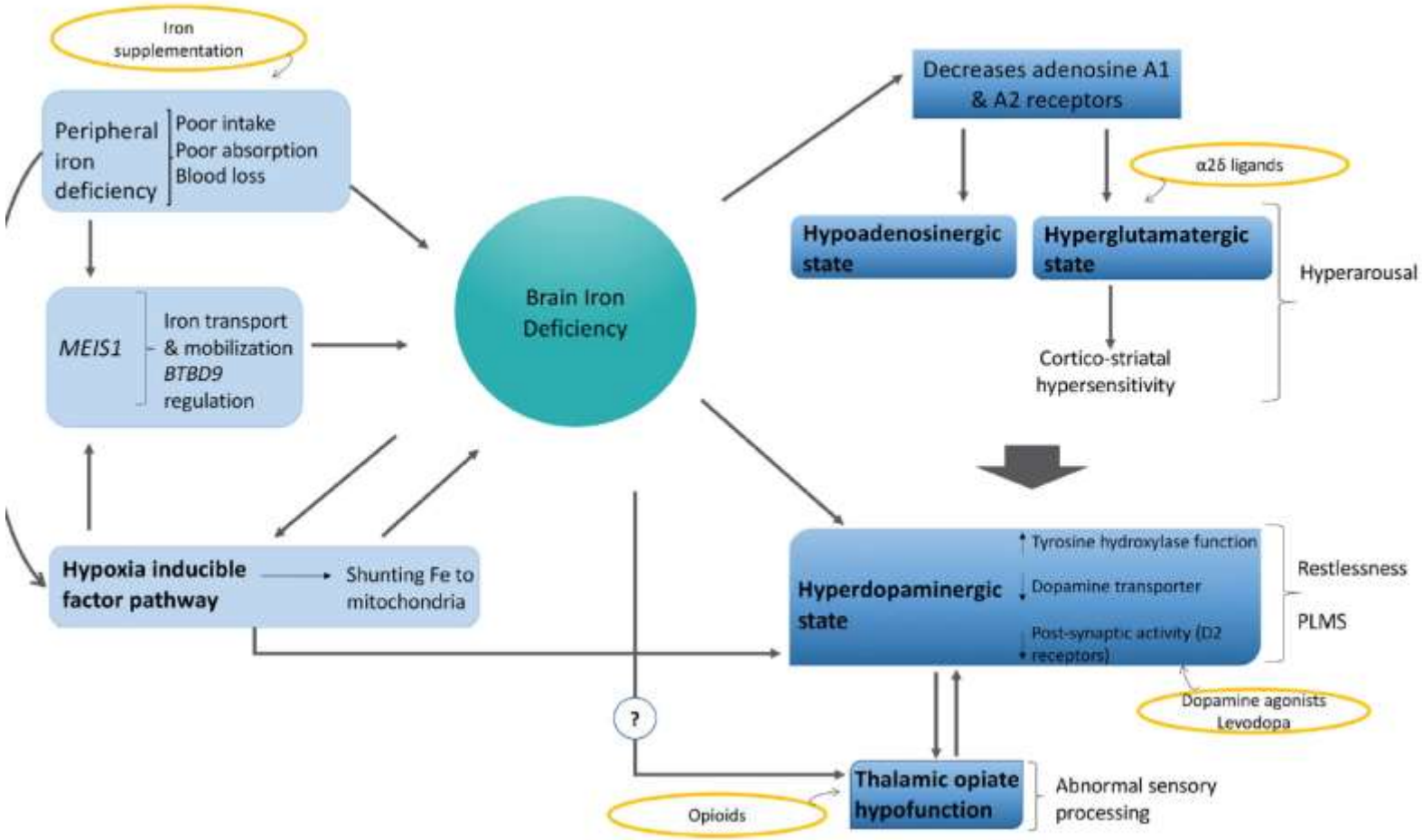


Current Neurology and Neuroscience Reports (2019) 19:54
https://doi.org/10.1007/s11910-019-0965-4

MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Update on Restless Legs Syndrome: from Mechanisms to Treatment

Paulina Gonzalez-Latapi [1] · Roneil Malkani [1,2]



RJS- patofüsioloogia

Dopamiinergilise süsteemi düsbilanss

Substantia nigra Fe sisalduse vähenemine

D2 tüüpi retseptorite aktiivsuse vähenemine

Suurenenud intratsellulaarne dopamiin

Dopamiini düsfunktsioon

RJS korral on vähenenud dopaminergiline signaal

- vähenenud dopamiini transporteri aktiivsus
- dopamiini tagasihaarde vähenemine
- dopamiiniretseptorite regulatsioon jõuab öösel ja varahommikul madalaimale tasemele
- öine dopamiini aktiivsuse puudujääk

Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

Patofüsioloogia

Häirunud raua metabolism

perifeerne ja aju raua metabolism

- kellel on rauavaegusaneemia on RLS-i risk 5–6 korda kui kogu elanikkonnal
- raua transport ajju ning aju Fe säilitamine ja mobiliseerimine on häiritud

Mitme neurotransmitteri süsteemi häire

Opiaatide süsteemi häirumine

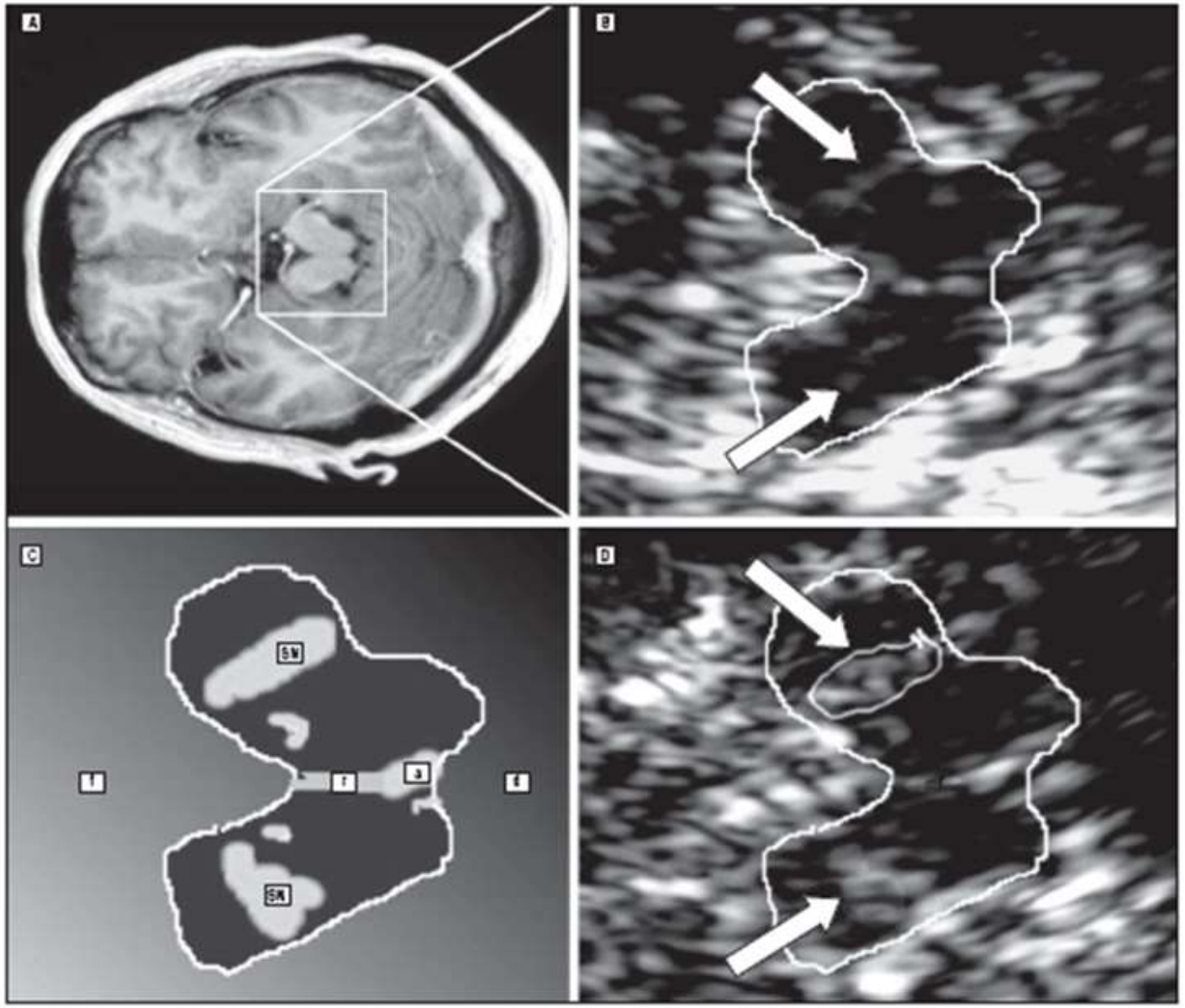
Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

Raud – mõistmaks RJS

Neurovisu tsiooni langust
s. nigra's,

Aju raua biliseerimisest või
säilitam

- *H-fe pordis*
- *H-fe ähenemisele*



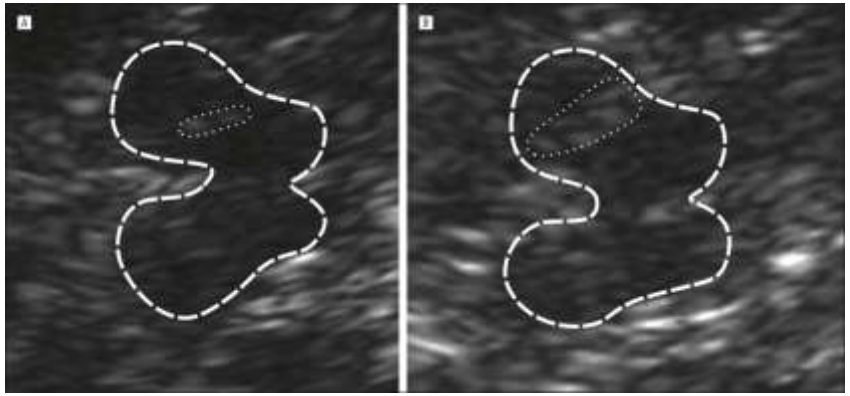
Peeraully and Tan *Translational Neurodegeneration* 2012, **1**:6
http://www.translationalneurodegeneration.com/content/1/1/6

Translational Neurodegeneration

REVIEW Open Access

Linking restless legs syndrome with Parkinson's disease: clinical, imaging and genetic evidence

Tasneem Peeraully and Eng-King Tan*



RJS- patofüsioloogia

Raua a/v häirumine

1. Mida varasem haiguse algus, seda madalam raua tase KNS's
2. Ferritiin < 45 µg/l on sümptomaatika kõige raskem
3. Fe taseme ööpäevane kõikumine põhjustab sümptomite rütmilisuse
4. Fe defitsiidi korral striatumis D retseptorite alaregulatsioon
5. Üld Fe on normis

Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

Opioidiretseptorid

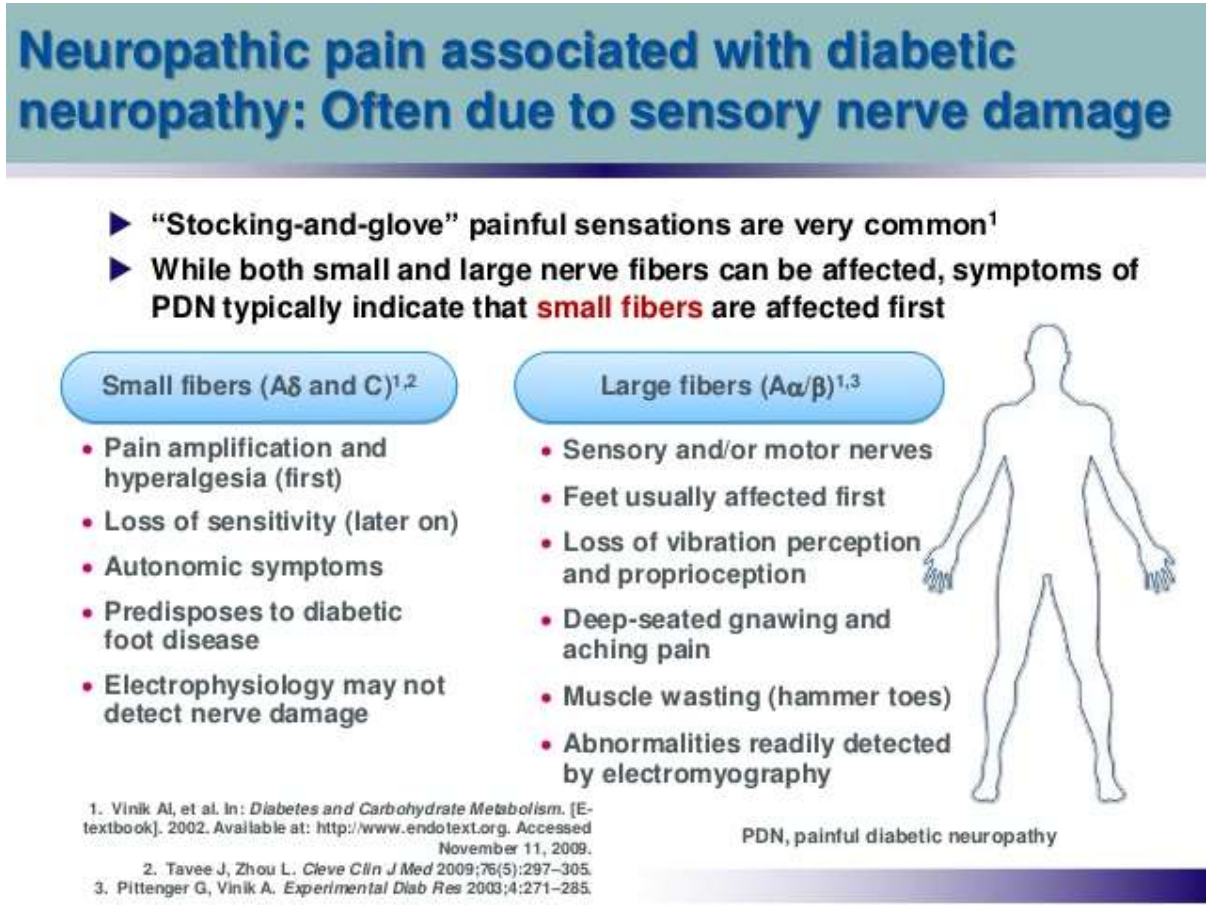
- Opioidretseptorite blokk võib esile kutsuda RLSi
- Opioidid võivad parandada RJS
- Endogeenne opioidpuudulikkus võib põhjustada RJS-i
- Opioidid interakteeruvad ka dopaminergilise süsteemiga

Hortensia Alonso-Navarro, Elena García-Martín, José A.G. Agúndez, et al. Neurology, 2019

Sensoorse süsteemi haaratus RJS korral ?

PERIFEERNE v. TSENTRAALNE

- Suured kiud
- Väikesed kiud



Ravi

Drug	Starting dose and maximum recommended dosage	Time to full effective therapeutic dose	Half-life	Side effects
Levodopa	50 mg 200 mg	At first dose	1.5-2 hours	Augmentation Rebound
Ropinirole	0.25 mg 4 mg	4-10 days	6 hours	Nausea, low blood pressure, dizziness, headache, nasal congestion
Pramipexole	0.125 mg 0.54 mg	At first dose	8-12 hours	Nausea, low blood pressure, dizziness, headache, nasal congestion
Rotigotine	1-3 mg patches	1 week	5-7 hours	Skin irritation, nausea, low blood pressure, dizziness, headache, nasal congestion
Pregabalin	25-300 mg	3-6 days	10 hrs	Sleepiness, dizziness, headache, fluid retention
Clonazepam	0.50 mg 2.0 mg	First dose: effect mainly on sleep	30-40 hours	Sleepiness, dizziness, morning drug hangover
Gabapentin	300 mg 2700 mg	3-6 days	5-7 hours	Sleepiness, dizziness, fluid retention

Garcia-Borreguero *et al. BMC Neurology* 2011, **11**:28
http://www.biomedcentral.com/1471-2377/11/28