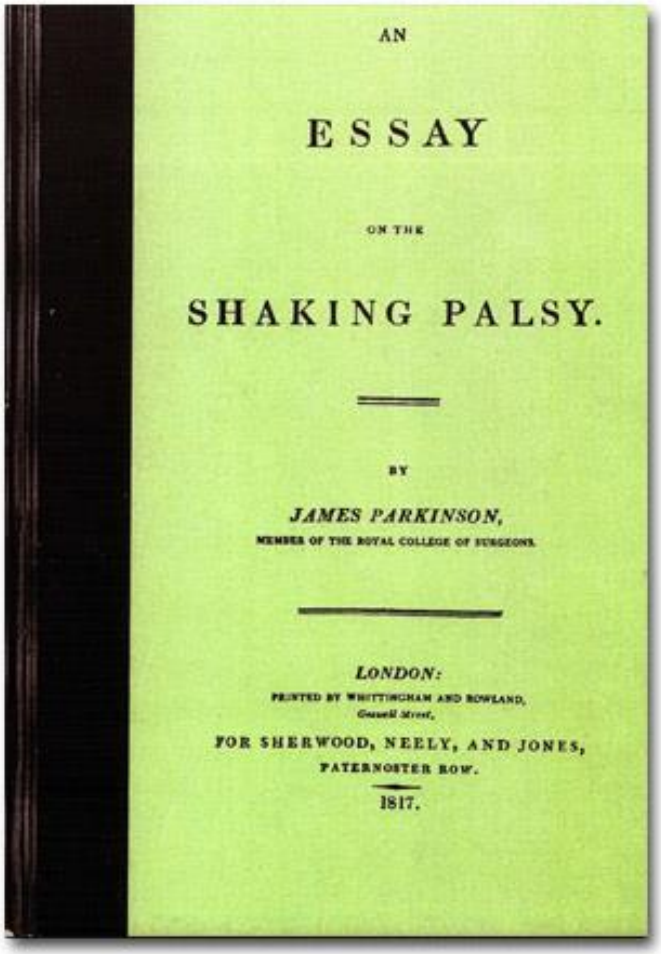
Extrapyramidal (Movement) disorders

Matej Skorvanek MD PhD
Dept. of Neurology



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Idiopathic Parkinson's disease (80%)

Symptomatic secondary parkinsonism (10%)

- Drug-induced
- Toxic – M.Wilson, Mn, CO, MPTP
- Traumatic
- Vascular
- Parkinsonian syndrome in normal-pressure hydrocephalus

Neurodegenerative parkinsonian syndromes (10%)

- Multiple system atrophy
- Progressive supranuclear palsy
- Corticobasal degeneration
- Dementia with Lewy bodies

Pathology of neurodegenerative parkinsonism

Synucleinopathies	Tauopathies
• Parkinson's disease • Parkinson's disease with dementia • Lewy body dementia •Multiple system atrophy	• Progressive supranuclear palsy • Corticobasal degeneration • Frontotemporal lobar degeneration

Parkinson’s disease - definition

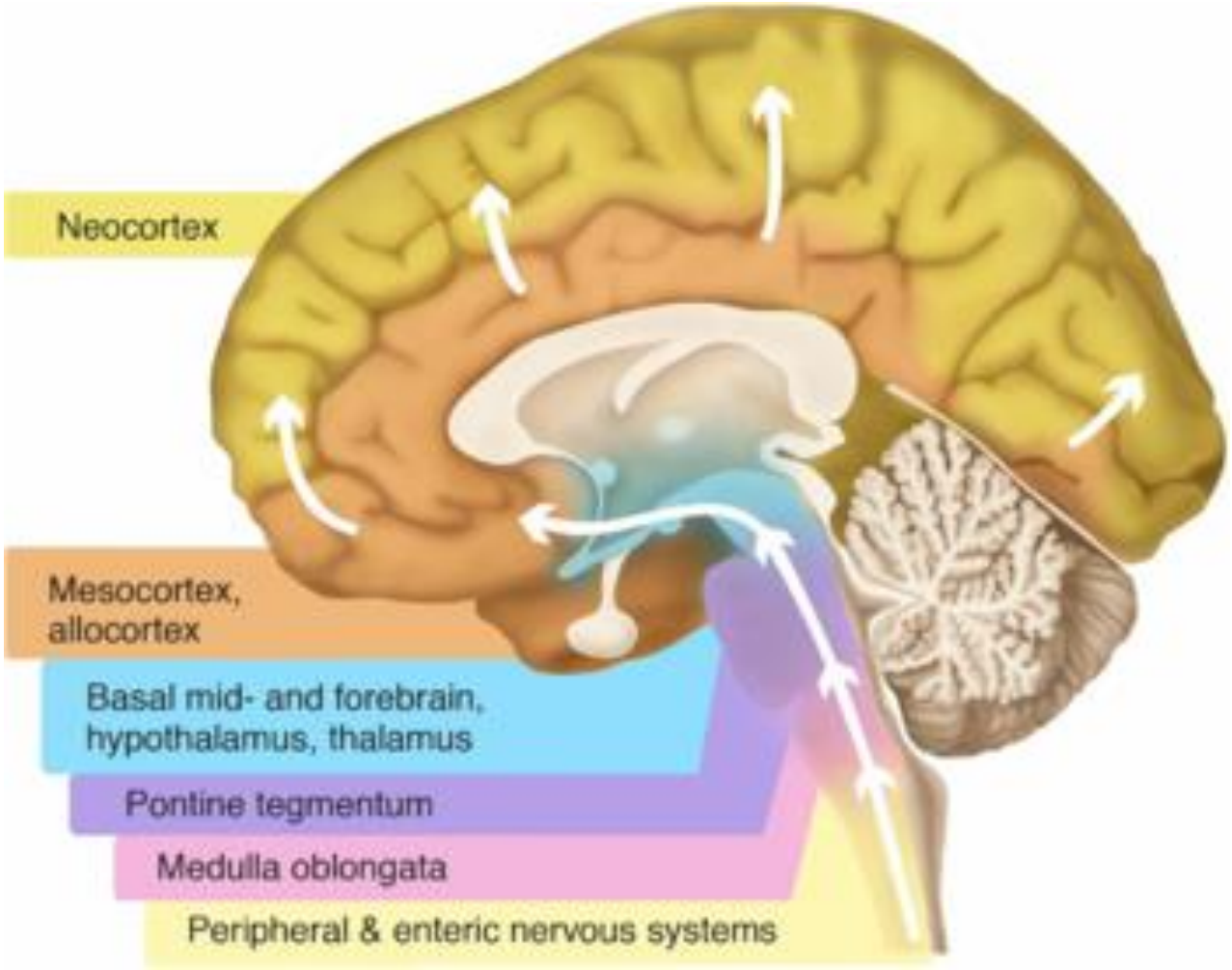
- Chronic progressive neurodegenerative disease affecting central and peripheral nervous system and other organs

- Loss of nigrostriatal neurons and presence of intracelular inclusions containing α-synuclein - Lewy bodies and Lewy neurites

Epidemiology

- Prevalence 100-300/100 000
- Prevalence at the age of 60 years 1%
- Prevalence at the age of 85 years 3-5%
- Incidence 8-19/100 000
- Clinical manifestation typically at the age of 45-75 years
- 5-10% cases onset before the age of 40
- Europe ♂:♀=1,5:1
- Hispanic white > non-hispanic white > asian > black

Pathology – Braak hypothesis

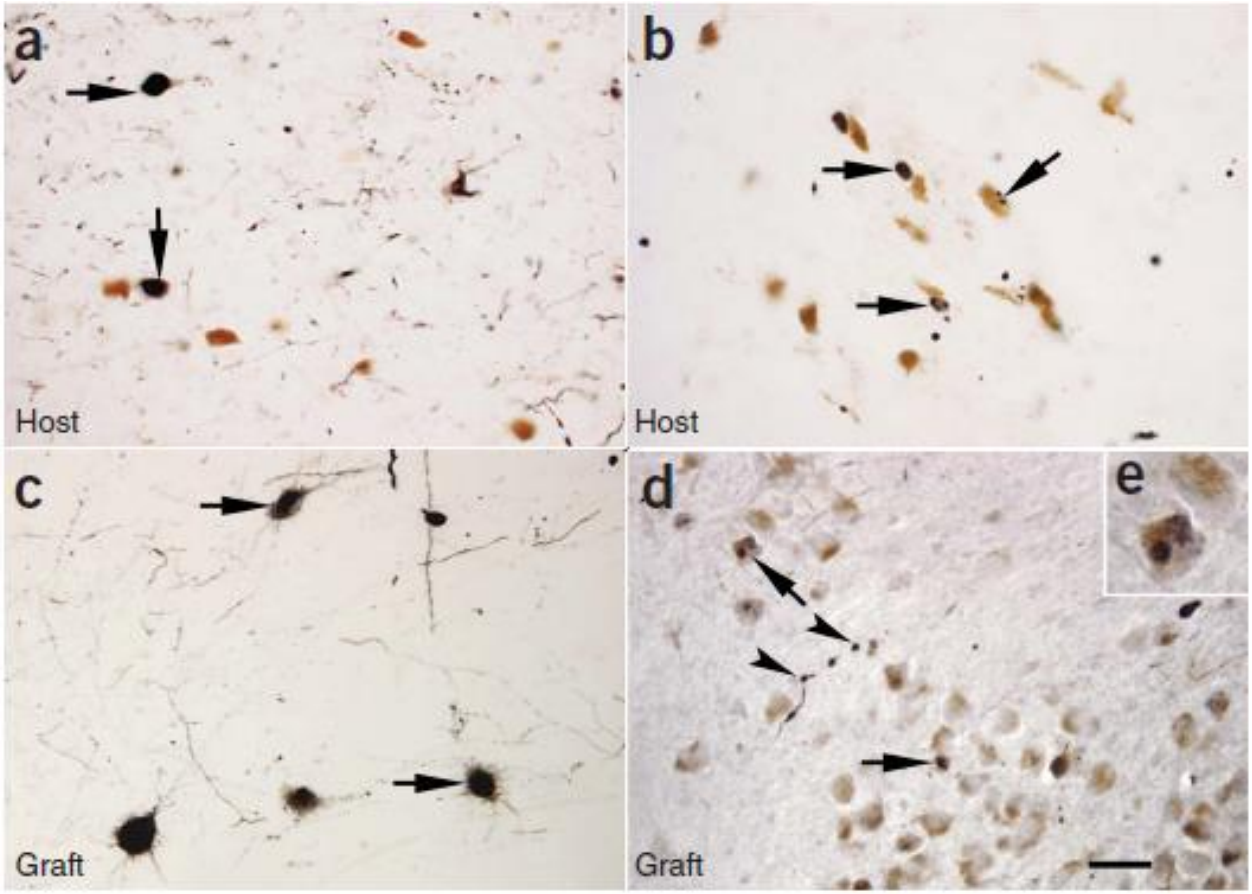


Visanji 2013

Etiopathogenesis

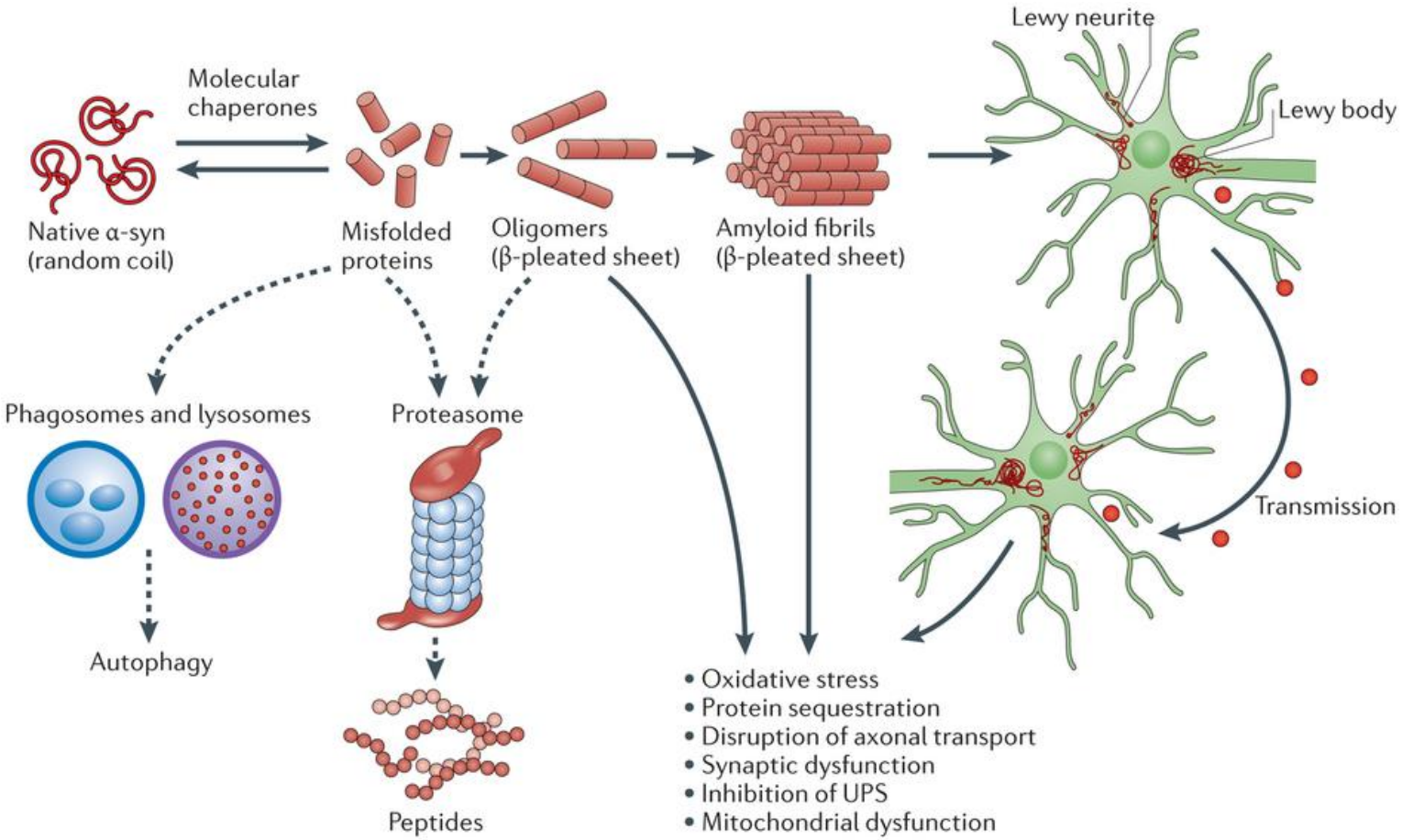
- Multifactorial
- Monogenic forms of PD 10-15% (AR - parkin, AD – LRRK2)
- Idiopathic PD 85-90%
  - Endocellular factors
    - Mitochondrial dysfunction
    - Dysregulation of Calcium homeostasis
    - Lysosomal dysfunction, autophagy abnormalities

Prion-like mechanism of a-synuclein spreadin in PD?



Korodower, Nat Med 2008

Mechanism of a-synuclein spreading?



Nature Reviews | Neuroscience

Irwin et al., Nat Rev Neurosci 2013

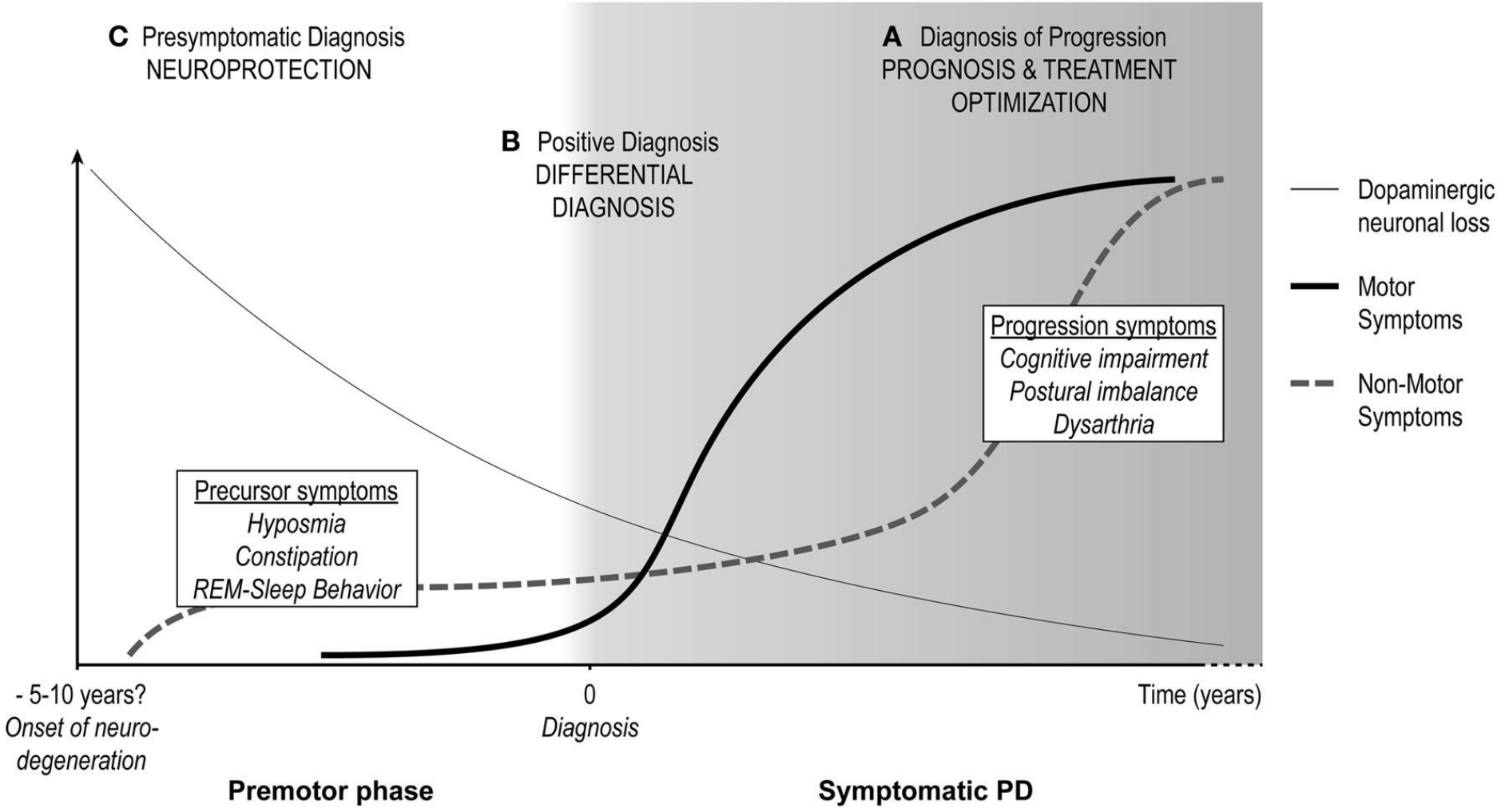
Spreading of a-synuclein

- Spreading proved in:
  - Cell cultures
  - After intra-striatal injection of pathological a-syn oligomers
  - After injection of pathological a-syn oligomers in vagus nerve
  - Spreading from the gut in rotenone model of parkinsonian mice

  - Involvement of immune system? (LAG3 receptors, etc)

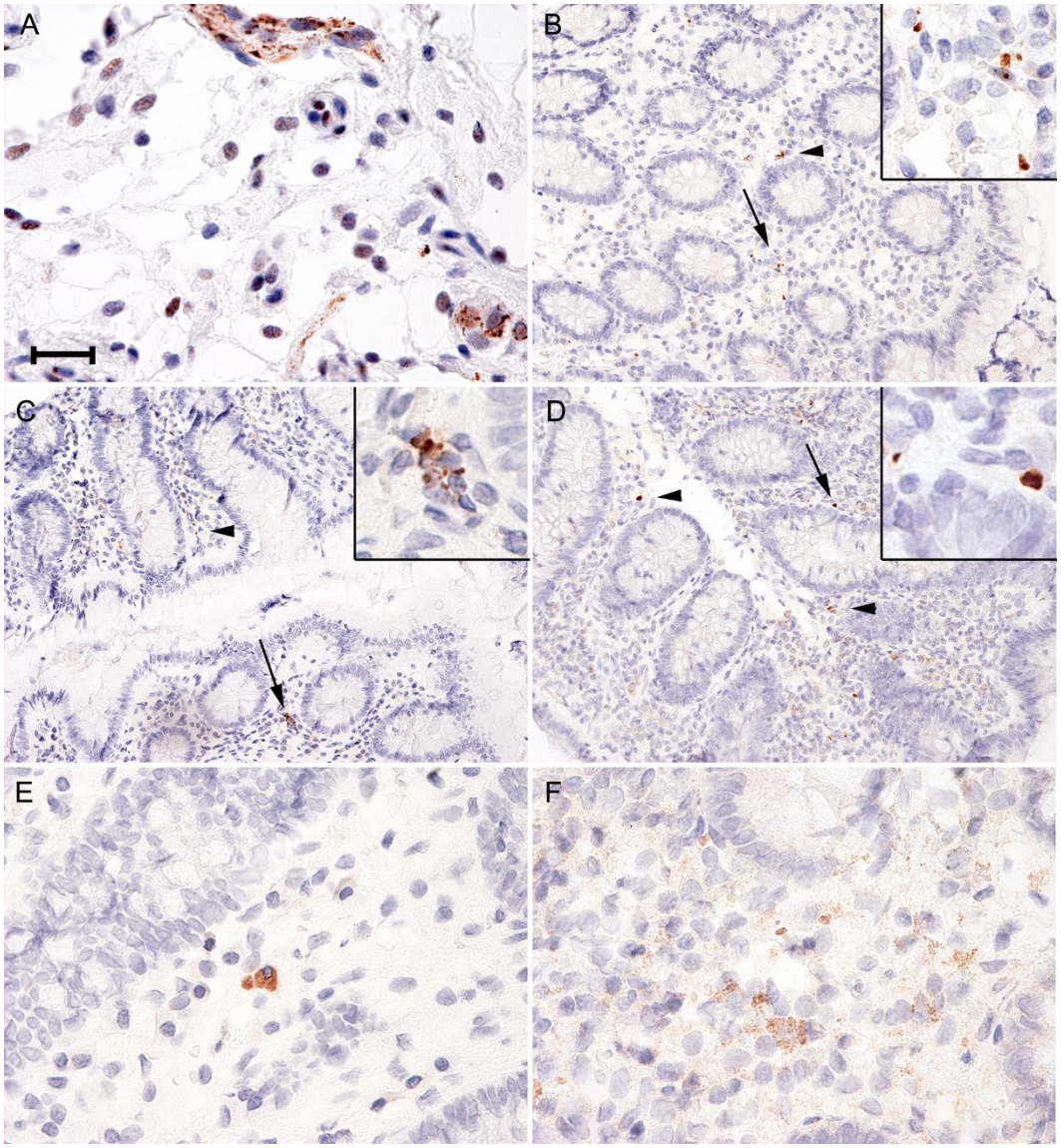
Hansen 2011, Luk 2012, Pan-Montojo 2014, Mao 2016

Biomarkers in Parkinson's Disease: What For?



Lebouvier 2010

Proof of a-syn presence in the enteric nervous system



Skorvanek et al. Mov Disord 2018

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

- Bradykinesia/akinesia – most important feature (present in 100% of cases)

+at least one of the following

  - Rigidity
  - Resting tremor

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease

☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y

☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system

☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Once presence of parkinsonism was established

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Motor symptoms

Well treatable

- Bradykinesia
- Rigidity
- Tremor
- Off freezing
- Off dystonia

Poorly treatable

- Postural instability
- Speech problems
- Dysphagia
- On freezing
- On dystonia

Non-motor symptoms of PD(NMS)

Neuropsychiatric symptoms	Sleep problems
Depression Anxiety Apathy Hallucinations, delusions, illusions Delirium (may be drug-induced) Cognitive impairment (Dementia, MCI) Dopamine dysregulation syndrome Impulse control disorders Panic attacks (could be “off” related)	REM sleep behaviour disorder (possible pre-motor) Excessive daytime somnolence, narcolepsy type “sleep attack” Restless legs syndrome, periodic leg movements Insomnia Sleep disordered breathing Non-REM parasomnias (confusional wandering)

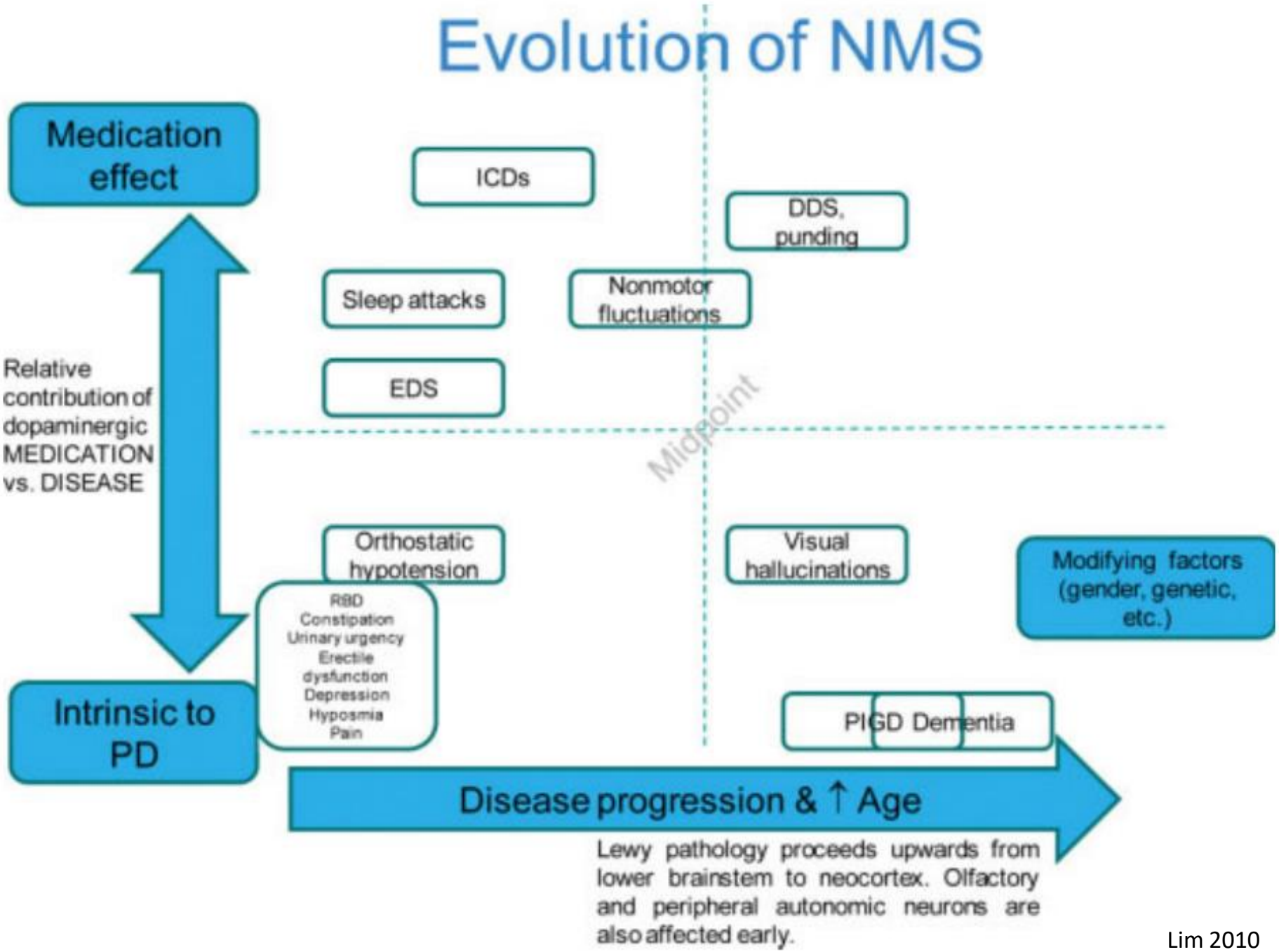
Fatigue	Sensory symptoms
Central fatigue (maybe related to dysautonomia) Peripheral fatigue	Pain Olfactory disturbance Hyposmia Functional anosmia Visual disturbance (blurred vision, diplopia), impaired contrast-sensitivity

Chaudhuri K.R. et al., Parkinson’s disease: The non-motor issues, *Parkinsonism & Related Disorders*, In Press, Corrected Proof, xxx 2011, 1-7

Autonomic dysfunction	Gastrointestinal symptoms
Bladder urgency, frequency, nocturia Sexual dysfunction (may be drug-induced) Sweating abnormalities (hyperhidrosis) Orthostatic hypotension	Dribbling of saliva Dysphagia Ageusia Constipation Nausea Vomiting Reflux Fecal incontinence
Dopaminergic drug-induced behavioural NMS	**Dopaminergic drug-induced "other" NMS**
Hallucinations, psychosis, delusions Dopamine dysregulation syndrome (usually linked to levodopa intake) Impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating)	Ankle swelling Dyspnoea (maybe linked to ergot dopamine agonist related cardiac/respiratory failure) Subcutaneous nodules (apomorphine) Erythematous rash (rotigotine patch)

Other symptoms	Non-motor fluctuations
Weight loss Weight gain (could be related to impulse control disorders)	Dysautonomic Cognitive/Psychiatric Sensory/Pain Visual blurring

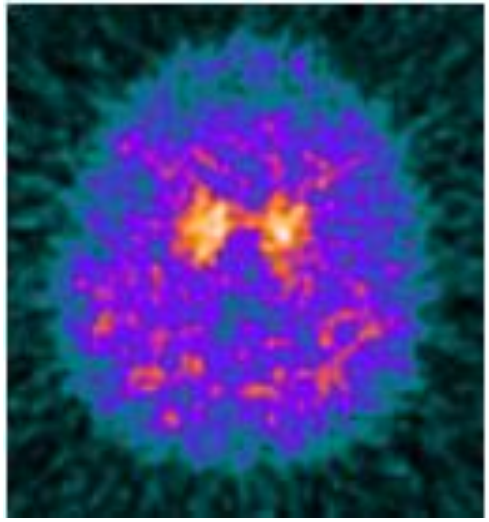
Chaudhuri K.R. et al., Parkinson's disease: The non-motor issues, *Parkinsonism & Related Disorders*, In Press, Corrected Proof, xxx 2011, 1-7


Evolution of NMS
Medication effect
ICDs
DDS, punding
Sleep attacks
Nonmotor fluctuations
EDS
Relative contribution of dopaminergic MEDICATION vs. DISEASE
Midpoint
Orthostatic hypotension
Visual hallucinations
Modifying factors (gender, genetic, etc.)
RBD
Constipation
Urinary urgency
Erectile dysfunction
Depression
Hyposmia
Pain
Intrinsic to PD
PIGD Dementia
Disease progression & ↑ Age
Lewy pathology proceeds upwards from lower brainstem to neocortex. Olfactory and peripheral autonomic neurons are also affected early.

Lim 2010

Neuroimaging

- Brain CT / MRI– standard examinations normal – usually performed to exclude other causes
- DaT scan – decreased binding of radiotracer (ioflupan) in presynaptic part of the nigro-striatal junction
  - Differentiates degenerative from non-degenerative
  - Does not differentiate PD from atypical parkinsonism



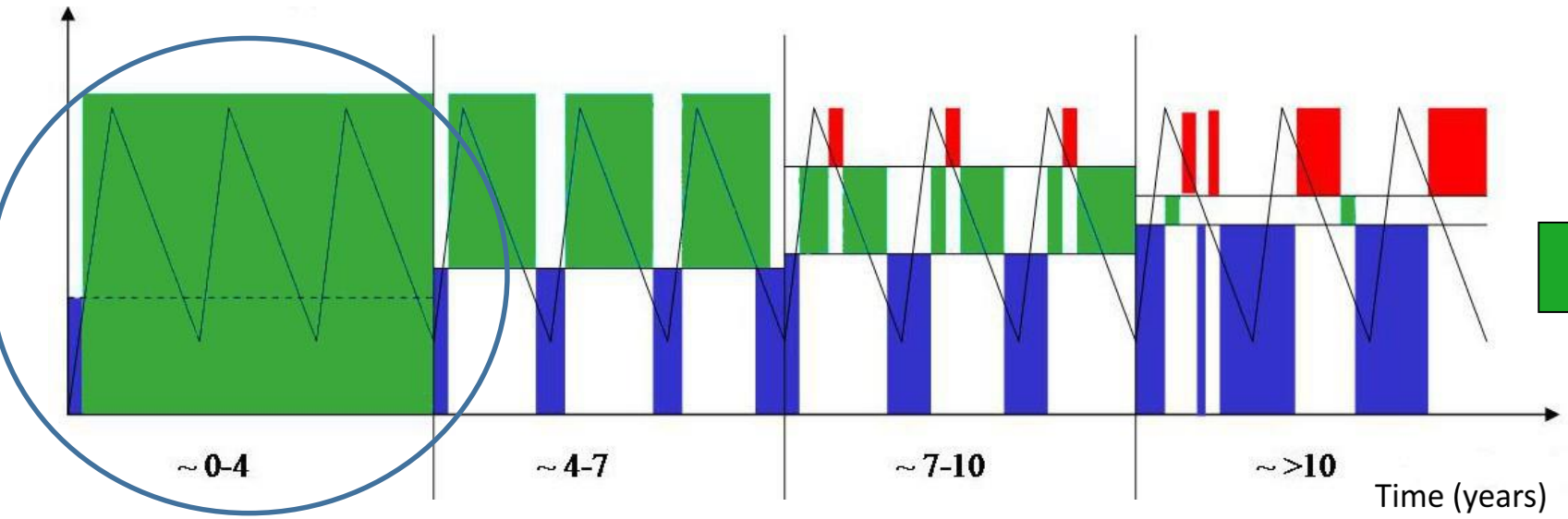
Disease course

- Preclinical stage (DaT SPECT, PET, transcranial USG, 7T MRI, genetics, biomarkers???, biopsy???)
- Premotor stage (hyposmia, obstipation, RBD, depression)
- Motor stage – „early stage“
- “Late stage” with motor and non-motor fluctuations and levodopa-resistant symptoms

Therapy

- Levodopa + carbidopa/benserazid
- Dopamine receptor agonists (non-ergot) – pramipexole, rasagiline, ropinirole
- Catechol-O-methyltransferase inhibitors (COMT) – entacapone / tolcapone
- Monoaminoxidase B inhibitors – Rasagiline/selegiline
- Amantadine
- Anticholinergics
- Domperidone (to decrease side effects of dopaminergic treatment)

PD disease course on treatment



Early stage

Good response to dopaminergic

Wearing-off

short off periods

treatment

Wearing –off with dyskinesias

Predictable peak-of-dose dyskinesias

On-off fluctuations

Unpredictable fluctuations

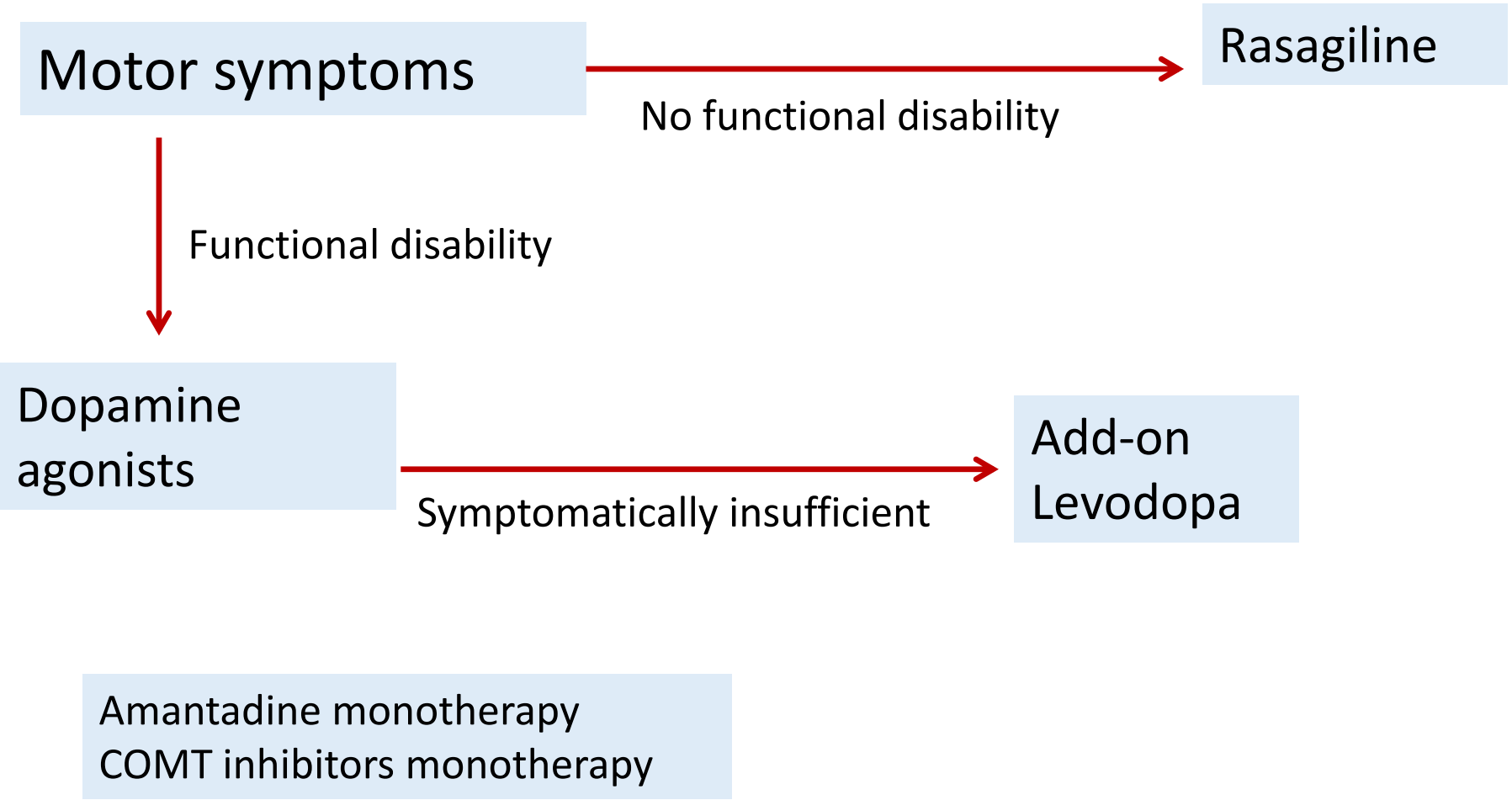
Very narrow therapeutic window

Normal mobility

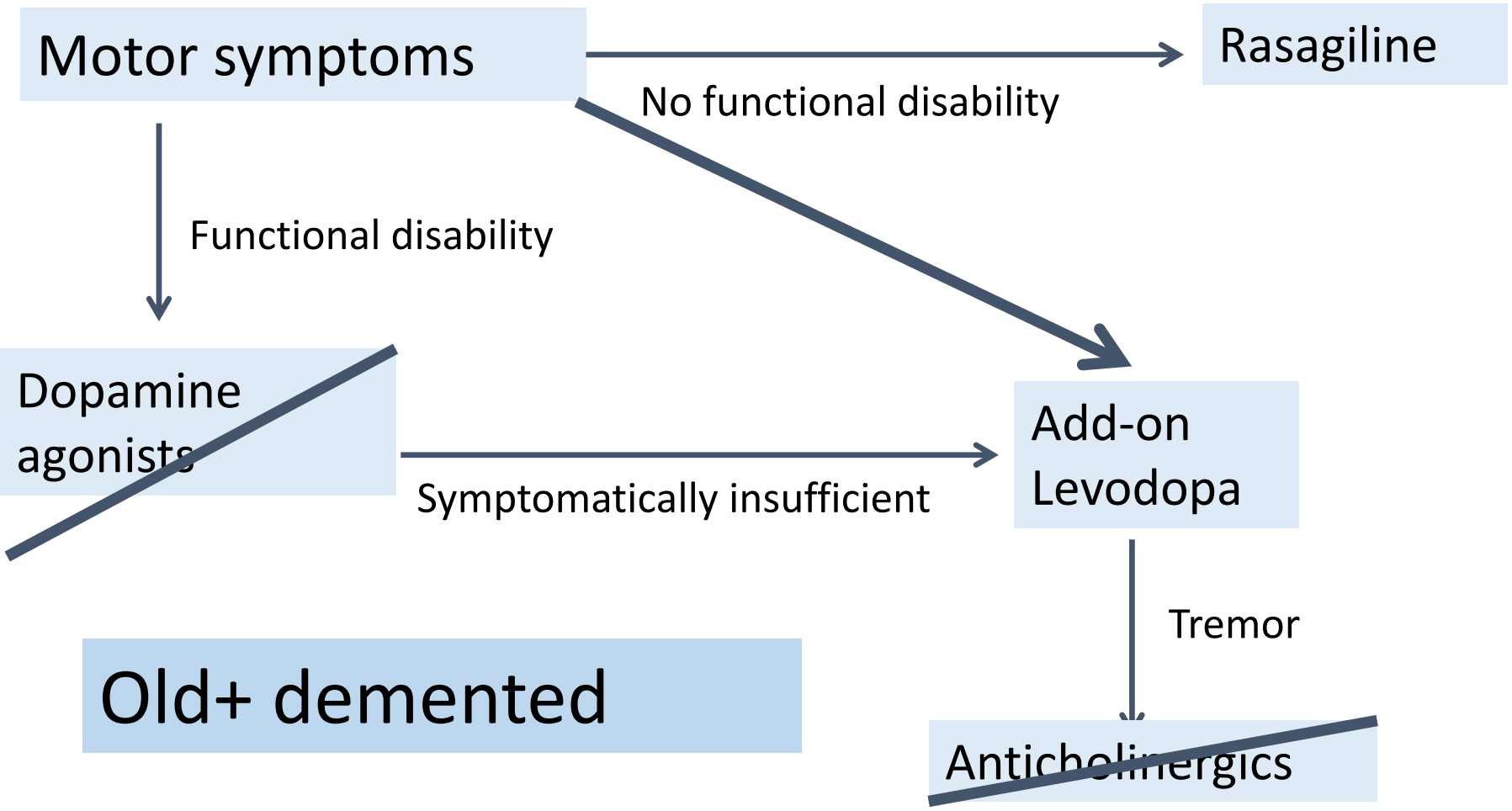
Parkinsonism

Dyskinesias

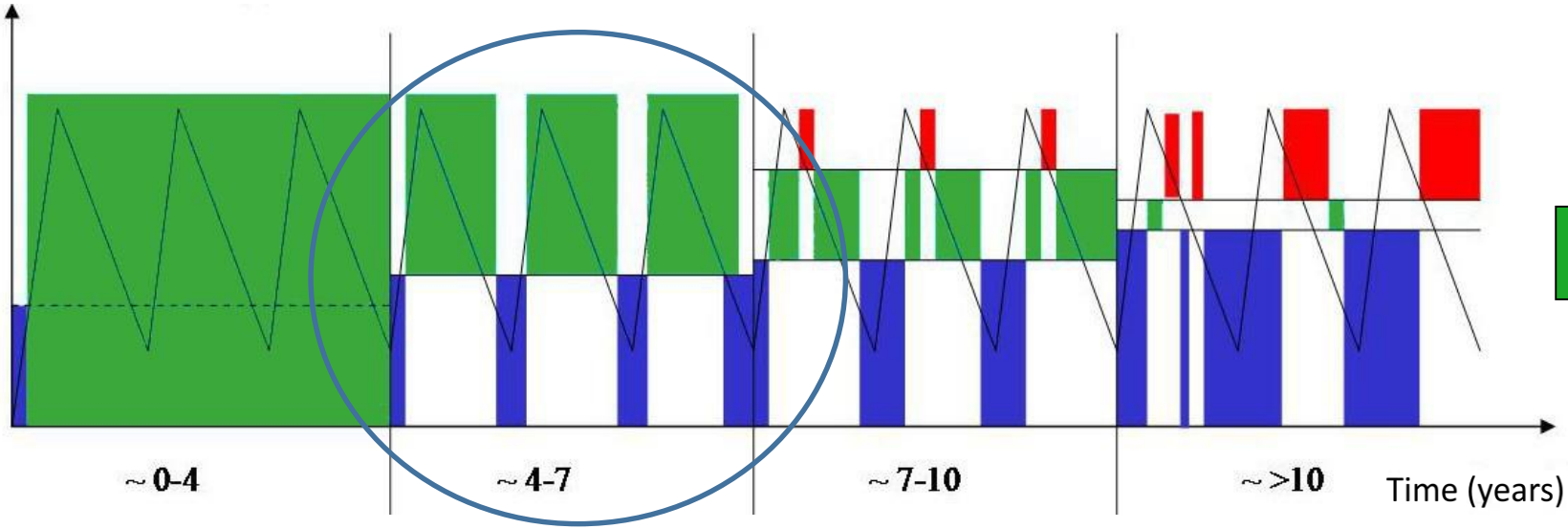
Rational pharmacotherapy of early PD



Rational pharmacotherapy of early PD



PD disease course on treatment



Therapeutic window

Eraly stage

Good response to dopaminergic

Wearing-off

short off periods treatment

Wearing –off with dyskinesias

Predictable peak-of-dose dyskinesias

On-off fluctuations

Unpredictable fluctuations

Very narrow therapeutic window

Normal mobility

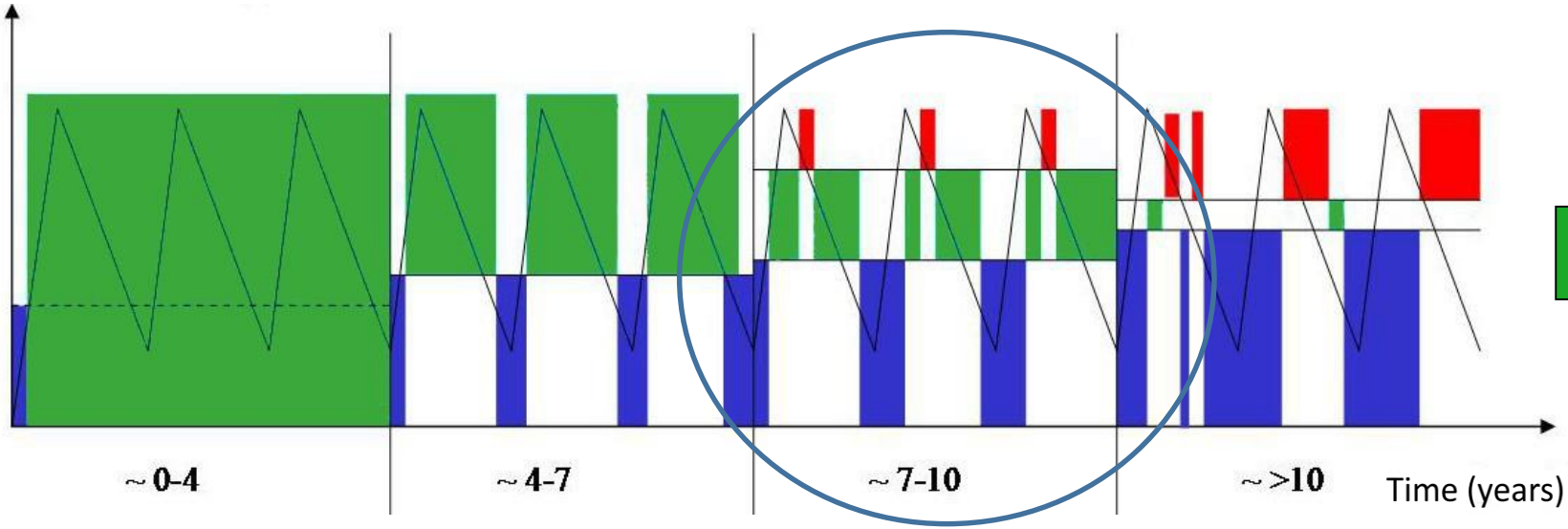
Parkinsonism

Dyskinesias

Wearing off - strategy

1. Increase the dose of dopamine agonists
2. Increase frequency of levodopa administration
3. Add-on COMT inhibitor
4. Add-on MAO-B inhibitor

PD disease course on treatment



Eraly stage

Good response to dopaminergic

Wearing-off

short off periods treatment

Wearing –off with dyskinesias

Predictable peak-of-dose dyskinesias

On-off fluctuations

Unpredictable fluctuations

Very narrow therapeutic window

Normal mobility

Parkinsonism

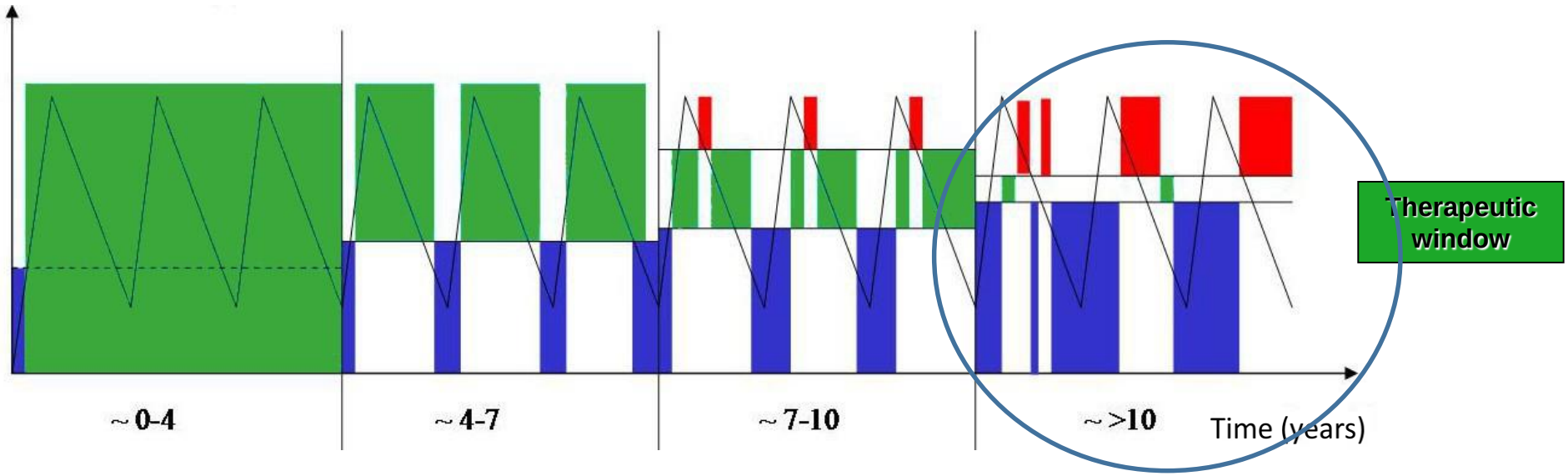
Dyskinesias

Peak-of-dose dyskinesias - strategy

1. Administration of levodopa more frequently and in lower doses

2. Add-on amantadine

PD disease course on treatment



Eraly stage

Good response to dopaminergic

Wearing-off

short off periods treatment

Wearing –off with dyskinesias

Predictable peak-of-dose dyskinesias

On-off fluctuations

Unpredictable fluctuations

Very narrow therapeutic window

Normal mobility

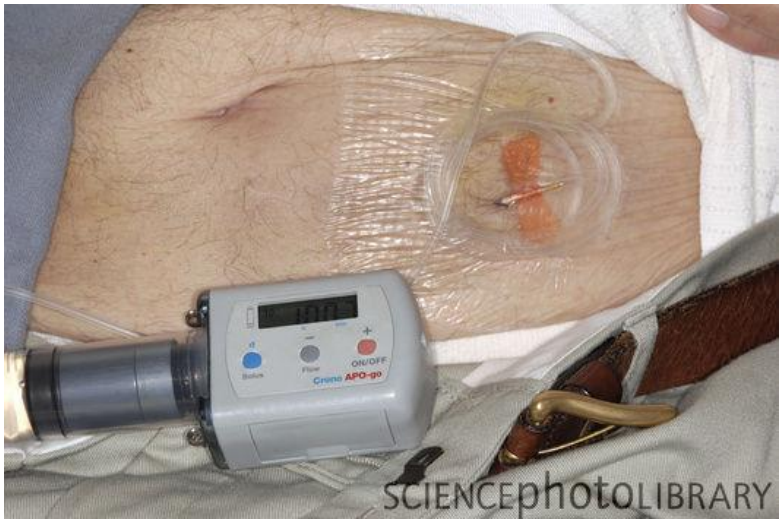
Parkinsonism

Dyskinesias

- Apomorphine – pen / pump
- Duodopa – continuous intrajejunal pump application of levodopa gel via PEG
- Deep brain stimulation

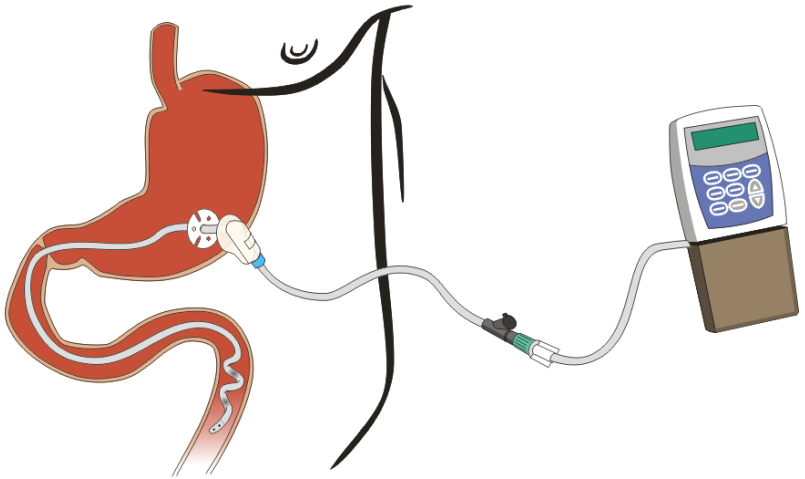
Apomorphine

- Dopamine receptor agonist
- Very short plasmatic half-life
- Rapid effect onset
- Pen / pump
- Nausea, vomitus
- Ortostathic hypotension
- Psychosis
- Impulse control disorder
- Production of subcutaneous nodules



What is Duodopa?

- Continuous intestinal application of levodopa gel
- Administration via a portable CADD® LEGACY pump

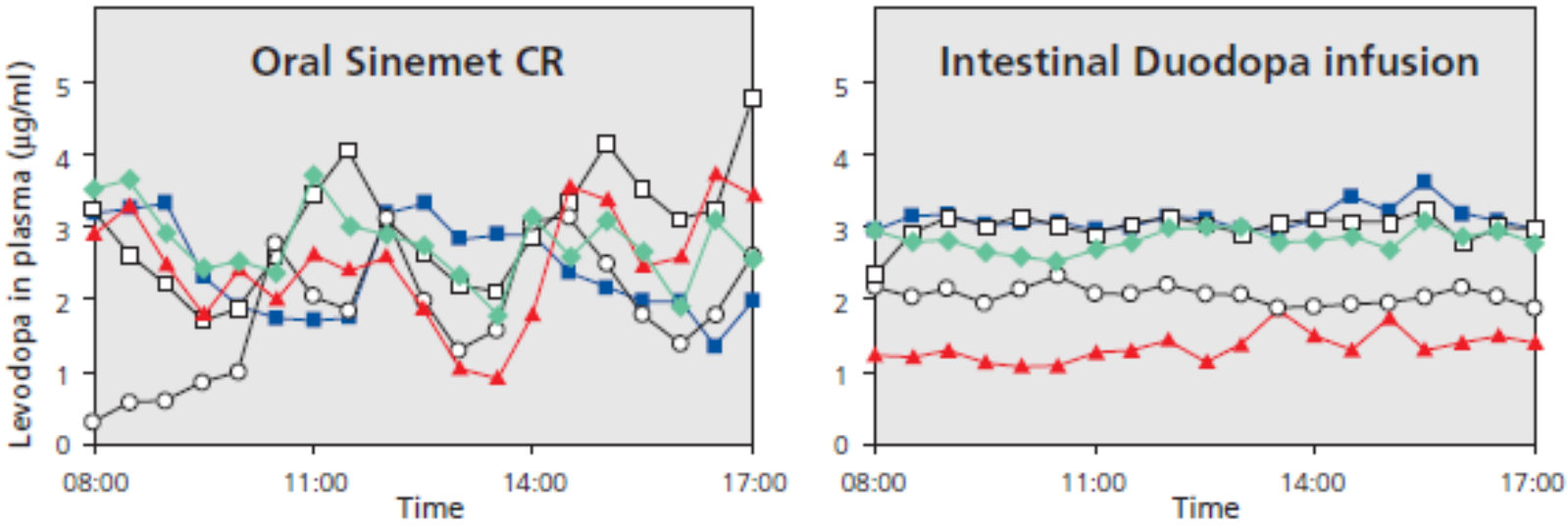


Clinical Neuropharmacology
Vol. 26, No. 3, pp. 156–163

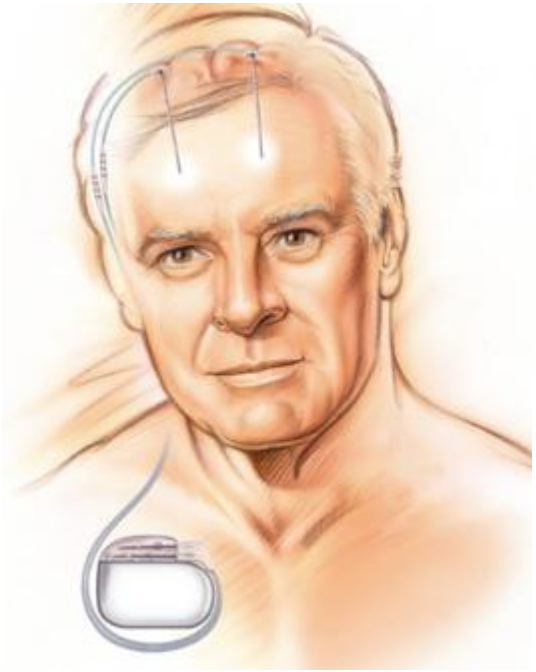
Optimizing Levodopa Pharmacokinetics: Intestinal Infusion Versus Oral Sustained-Release Tablets

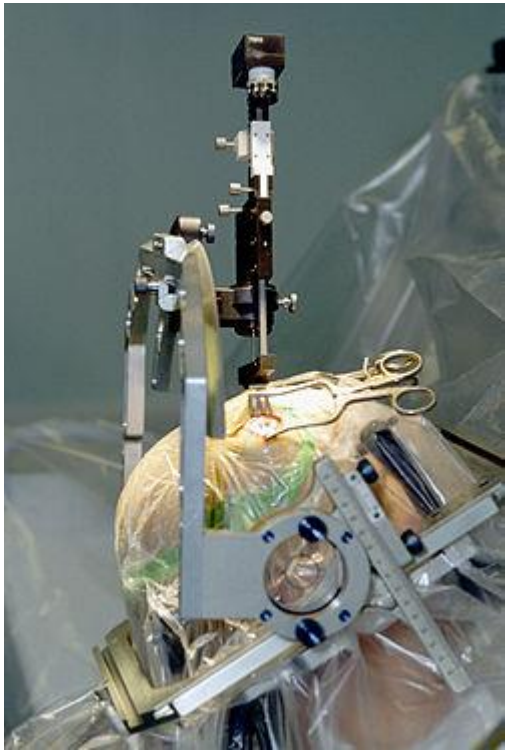
*Dag Nyholm, *Håkan Askmark, *Cecilia Gomes–Trolin, †Tina Knutson, ‡Hans Lennernäs, ‡Christer Nyström, and *Sten-Magnus Aquilonius

*Departments of *Neuroscience, Neurology, †Surgery, and ‡Pharmacy, Uppsala University, Sweden*



Deep brain stimulation- DBS

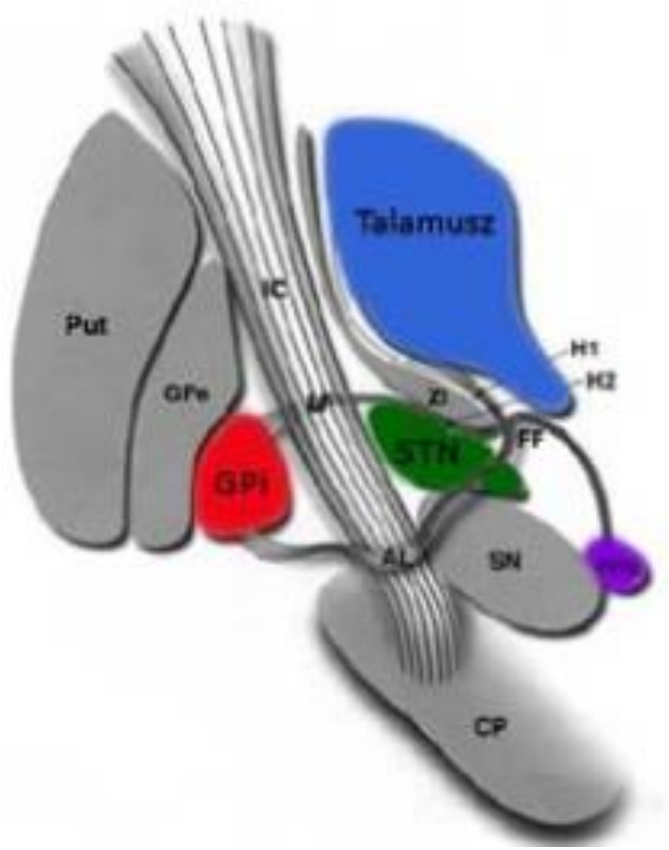




DBS targets

- Ncl. ventralis intermedialis thalami - VIM
  - tremor
- Zona incerta – ZI
  - tremor
- Globus pallidus internus - GPi
  - Dystonia
  - Parkinson’s disease
  - Gilles de la Tourette syndrome, chorea
- Nucleus subthalamicus - STN
  - Parkinson’s disease

DBS targets for PD



VIM thalamus
- Tremor reduction
- Minimal effect on bradykinesia and rigidity

Globus pallidus internus - GPi
- Fluctuations, dyskinesias
- Rigidity +-
- Tremor only mild

Subthalamic nucleus - STN
- Rigidity
- Bradykinesia
- Tremor
- indirectly dyskinesias

Prediction factors

- Younger age
- Shorter disease duration
- Excelent response in L-dopa test
- Good social background

- Presence of levodopa-resistant symptoms
- Preoperative cognitive defect
- Comorbidities (DM, cardial failure, stroke)
- Dopamine dysregulation syndrome
- Balance problems, dysartria

Acute complications vs. Chronic complications

- Bleeding
- Infection

- Cognitive decline
- Psychosis
- Depression and apathy (related to decreasing of medication)
- Worsening of speech
- Worsening of gait and balance

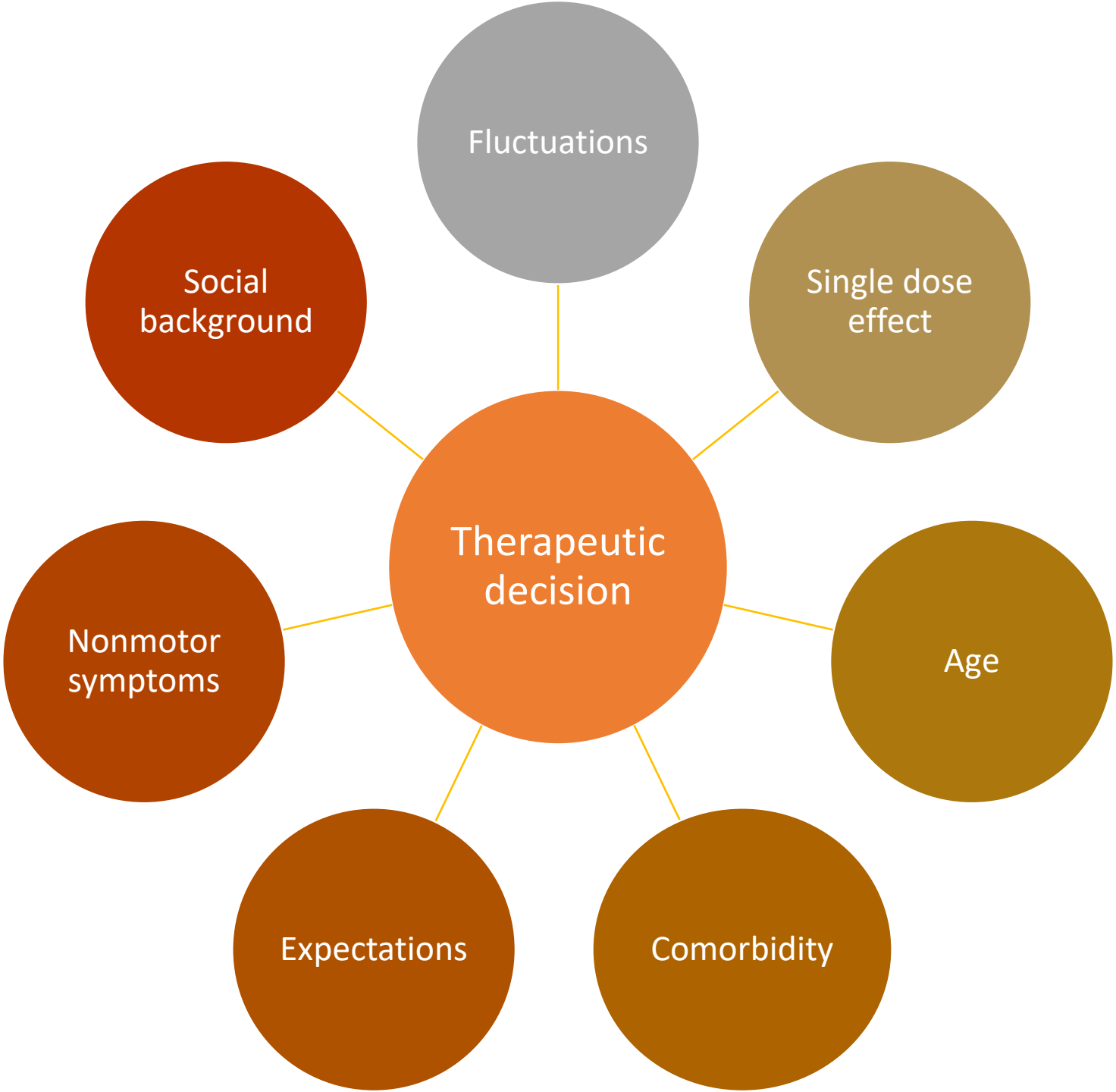
Treatment of NMS

- In year 2002 only 2 level A studies in PD related to treatment of NMS

- Psychosis: - clozapine
  - quetiapine (?)

- Dementia: - rivastigmine, donepezil,
  - memantine (?)

- Depression: - TCA v.s. SSRI
  - pramipexole?


Fluctuations
Social background
Single dose effect
Therapeutic decision
Nonmotor symptoms
Age
Expectations
Comorbidity

Essential tremor

- only tremor!!! (mostly on action)
- often positive family history
- usually excelent therapeutic response to alcohol
- 3x more frequent than PD

- Th: B-blockers (propranolol/metipranol), primidone, clonazepam, gabapentin, thalamic VIM deep brain stimulation

Atypical parkinsonism

- Rapid disease progression
- Usually suboptimal or no response to levodopa
- Atypical features
  - Early and severe frontal type of dementia
  - Other cortical dysfunction – apraxia, cortical sensitivity problem
  - Early dysphagia and dysartria
  - Autonomic dysfunction
  - Cerebellar symptoms
  - Supranuclear vertical gaze palsy
  - Early instability with falls

- Levodopa trial (up to 1000mg/day for 1 month) is always necessary

Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)

- 2. most frequent cause of neurodegenerative dementias (10-15%)
- Average survival 7 years
- DLB: dementia and parkinsonism occurred within 1 year from each other
- PDD: onset of dementia more than 1 year after the onset of parkinsonism

Central feature (essential for the diagnosis of possible or probable DLB):

- progressive cognitive deficit interfering with daily activities
- prominent defects in attention, executive functions and visuo-spatial functions
- Memory loss not necessarily present in early stages

Core feature:

- fluctuating cognition with pronounced variations in attention and alertness
- parkinsonism (75% of patients)
- visual hallucinations (46% - well formed and detailed)

Suggestive features:

- REM sleep behavior disorder
- hypersensitivity to neuroleptics
- low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

McKeith 2005

Multiple system atrophy (MSA)

- Sporadic neurodegenerative disorder with combination of autonomic dysfunction AND parkinsonism OR cerebellar symptoms
- prevalence 4,4/100 000
- Onset 5./6. decade
- Usual survival 6-9 years
- MSA-parkinsonism (60%)
- MSA-cerebellar variant (40%)

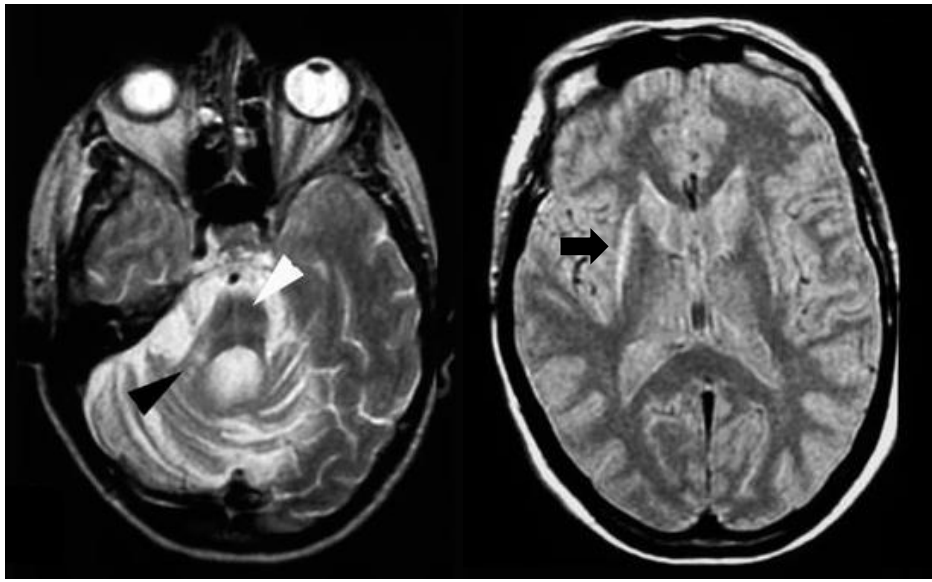
Consensus criteria for probable MSA

Sporadic progressive disorder with onset after the age of 30
Presence of autonomic dysfunction • urine retention/erectile dysfucntion • ortosthatic hypotension – decrement of >30/15 torr
AND
Parkinsonism
OR
Cerebellar syndrome

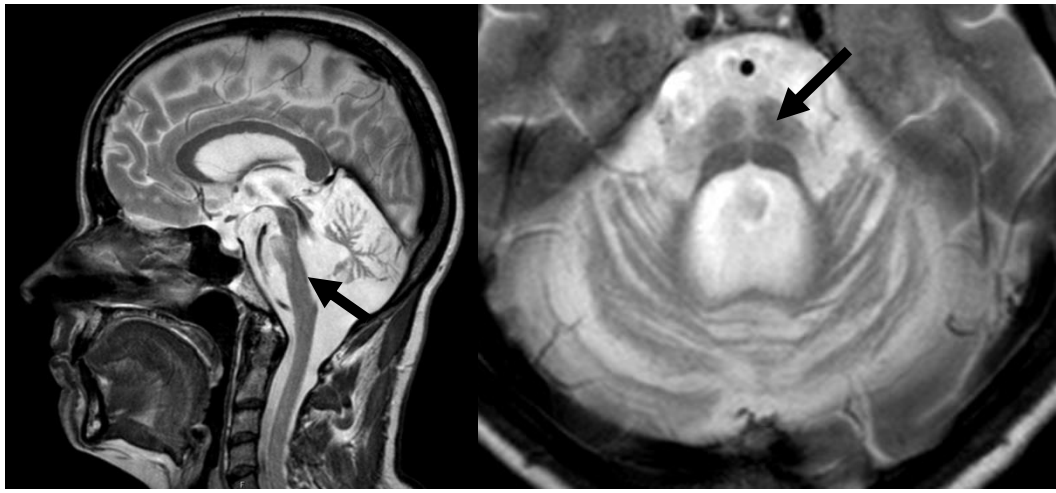
Gilman 2008

Neuroimaging

- MRI – 1.5T – putaminal hypointensity with hyperintense border (rim sign)
- MRI – 1.5T and 3T atrophy of pons, cerebellum a pedunculi cerebellares mediales, „hot cross bun sign“
- SPECT – normal MIBG uptake on myocardial scintigraphy
- Pathological DaT scan
- Pathological IBZM SPECT



1.5T MRI



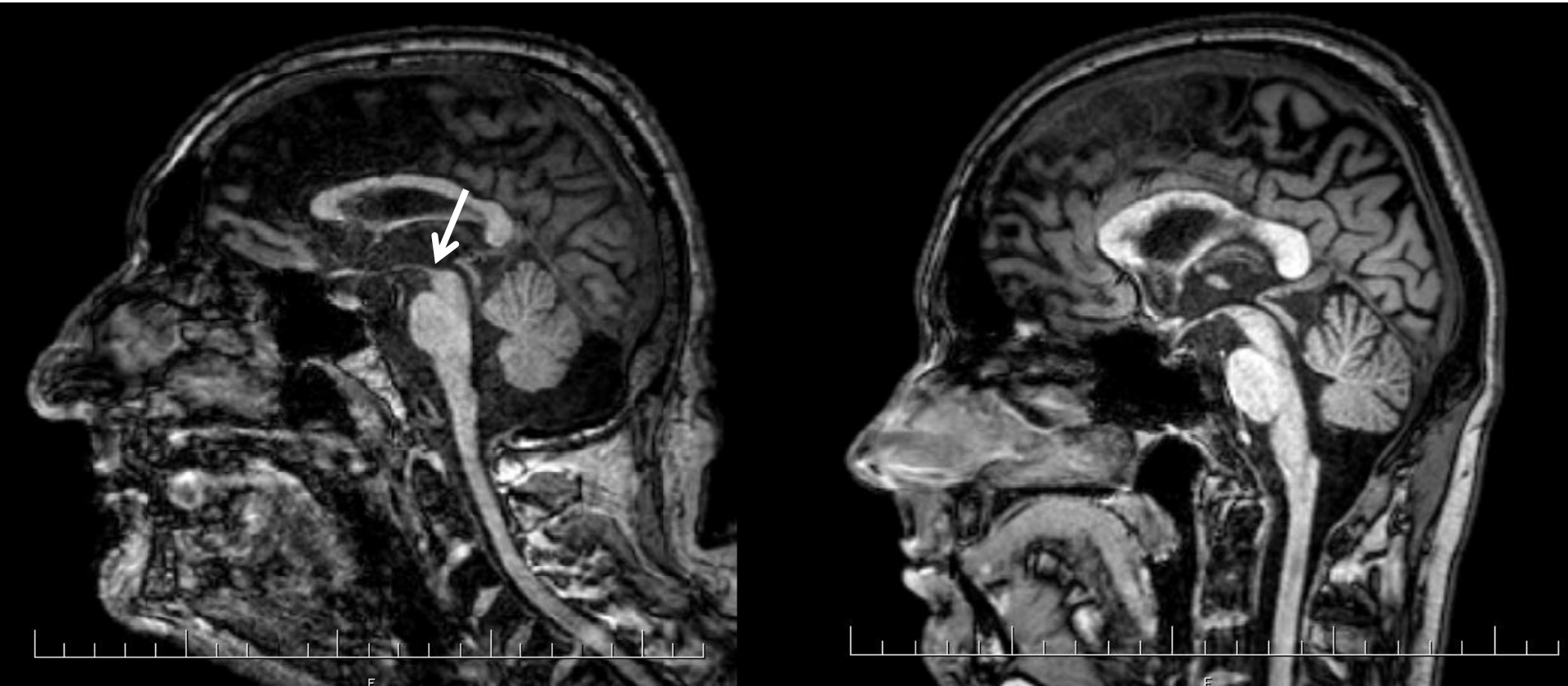
3.0T MRI

Progressive supranuclear palsy (PSP)

- progressive sporadic neurodegenerative disorder
- Presence of parkinsonism, supranuclear vertical gaye palsy, cognitive decline and early postural instability with early falls
- Onset after age of 40, usually 6./7. decade
- Prevalence: 1,3-4,9 / 100 000
- Survival: ± 6-10 rokov

Imaging

- MRI – „hummingbird/pinguin sign“
- DaT SPECT reduced presynaptic binding
- IBZM SPECT – reduced binding at postsynaptic D2 receptors



Corticobasal degeneration (CBD)

- Sporadic disorder, tauopathy
- Onset age 45-75 years
- Prevalence <1/100 000
- Asymmetric parkinsonism with deficits of higher cortical functions (mostly apraxia)

Klinické prejavy CBD

Cognitive decline	Speech disorder
• Executive dysfunction • Visuo-spatial dysfunction	• Can be independent from cognitive decline
Movement disorders	**Other cortical abnormalities**
Asymmetric parkinsonism Asymmetrická dystonia Tremor Myoclonus Gait disorder with early falls	• Apraxia • Alien limb phenomenon • Cortical sensitivity dysfunction
Insufficient levodopa response	

Therapy of atypical parkinsonism

Parkinsonism
- 1. Levodopa!!!!

Dystonia – if focal and bothersome
- Botulotoxín

Myoclonus
- Clonazepam

Tremor
- Anticonvulsives, propranolol?

Cognitive deficits
- In DLB – anticholinergics
- PSP, CBD – no effective treatment

Halucinations in DLB
- 1. anticholinergics
- 2. neuroleptics – only clozapine or quetiapine!!!!!

Physiotherapy and speech therapy

Paliative therapy

Dystonia

- Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned and twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese 2013

Phenomenology

- Fixed dystonia
- Mobile dystonia
- Dystonic tremor
- Dystonic myoklonus
- Dystonic „overflow“
- Geste antagoniste

Diamond 2006, Anheim 2006, Edwards 2011

Dif.dg. of dystonia

- Chorea – involuntary, unpredictable
- Tics – partially supressible, preceded by urge
- Spasticita – increased muscle tone, not posture – can be felt, not seen (abnormal posture due to spasticity – spastic dystonia)
- Stiff person syndrome – hypertonus predominantly of axial muscles
- Myotonia – disorder of muscle decontraction
- Tetanic syndrome
- Gegenhalten – voluntary/involuntary muscle activity against exogenous strength (functional disorder)
- Others:
  - Fixed contractures
  - Arthrodesis

New clasification of dystonia

Axis I: Clinical characteristics

I. Clinical characteristics
   I. Age of onset
   II. Body distribution
   III. Progression in time
      I. Disease course
      II. Variability

II. Associated features
   I. Dystonia isolated or combined with another movement disorder
   II. Other neurological or systemic disorders

Axis II: Etiology

I. Pathology of nervous system
   I. Proof of degeneration
   II. Proof of structural (often static) lesion
   III. Without proof of degeneration or structural lesion

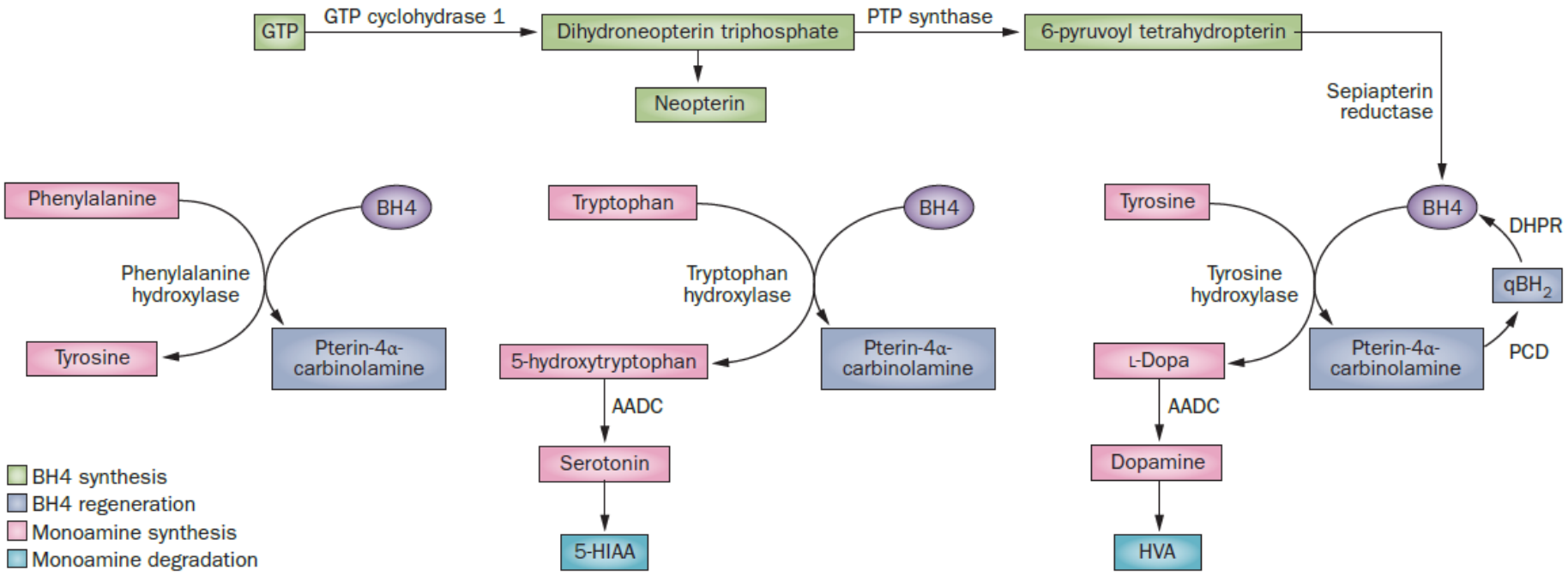
II. Inherited or acquired disorder
   I. Inherited
   II. Acquired
   III. Idiopathic

Cervical dystonia

- Most common dystonia, 9-10/ 100 000
- F>M, onset age typically 30-50
- Worsens on action, stress, sometimes spreading
- Often secondary neck pain
- Can be rather fixed, but often mobile with dystonic jerky tremor

Patient 2 – previous examinations

- Brain MRI – normal
- Brain MR spectroscopy – normal
- Metabolic exam – no specific abnormality
- Cardiologic examination – normal
- Phoniatric exam – normal
- Abdominal USG – normal
- Muscle enzymes – normal
- Genetic exam - „normal“
  - karyotype


GTP
GTP cyclohydrase 1
Dihydroneopterin triphosphate
PTP synthase
6-pyruvoyl tetrahydropterin
Neopterin
Sepiapterin reductase
Phenylalanine
BH4
Phenylalanine hydroxylase
Tyrosine
Pterin-4α-carbinolamine
Tryptophan
BH4
Tryptophan hydroxylase
5-hydroxytryptophan
Pterin-4α-carbinolamine
AADC
Serotonin
5-HIAA
Tyrosine
BH4
DHPR
Tyrosine hydroxylase
qBH2
L-Dopa
Pterin-4α-carbinolamine
PCD
AADC
Dopamine
HVA
BH4 synthesis
BH4 regeneration
Monoamine synthesis
Monoamine degradation

Dystonia Plus - Dopa-responsive dystonia (DRD)

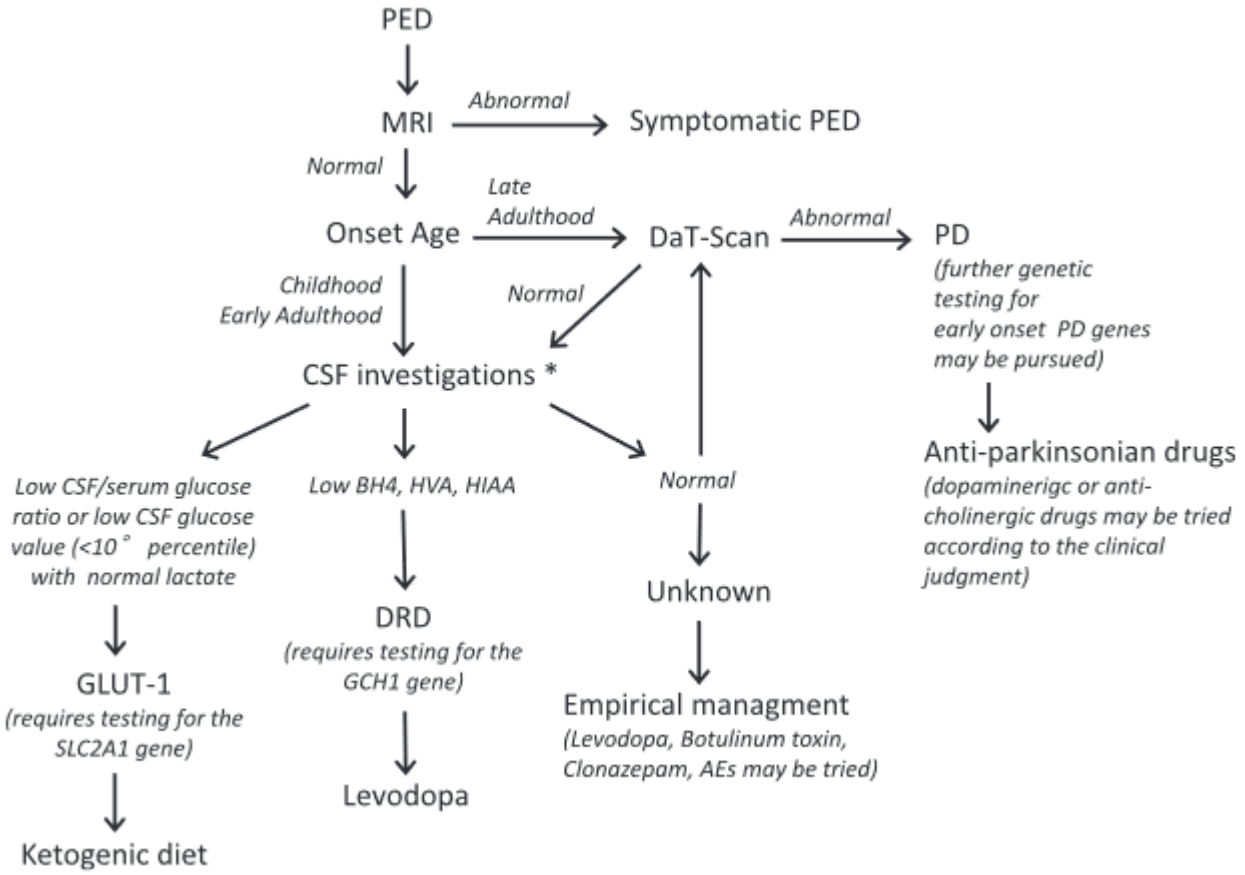
- Excelent response to L-dopa (200-400mg)
- AD with incomplete penetrance gene (GCH1), M:F=1:4
- Less frequently AR forms of disease – usually complicated – “DRD-plus”
- Problem in enzymatic production of levodopa
- Onset age 2-5 years
- Progressive leg dystonia+ parkinsonism, spasticity
- Diurnal fluctuations – worse in the evening
- Often misdiagnosed as cerebral palsy!!!!
- DaT scan negative
- Therapy – low doses of levodopa very effective, no motor fluctuations
- Every child with dystonia – Levodopa trial – up to 1000mg/day /1 month

- Paroxysmal kinesigenic dystonia (PKD)
- Paroxysmal non-kinesigenic dystonia (PNKD)
- **Paroxysmal exercise-induced dystonia (PED)**
- Normal finding between atacks
- Non-epileptic

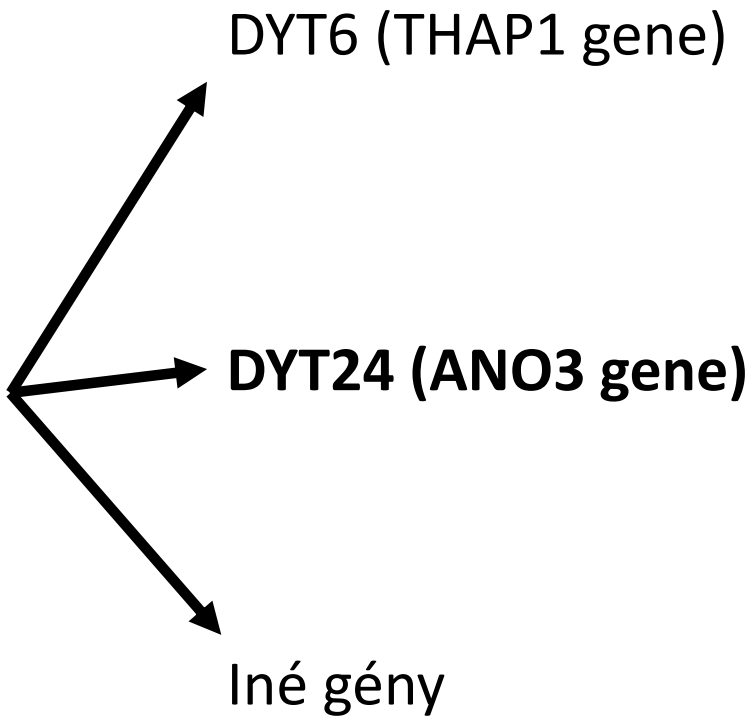
Movement Disorders
CLINICAL PRACTICE
ORIGINAL ARTICLE

The Clinical Syndrome of Paroxysmal Exercise-Induced Dystonia: Diagnostic Outcomes and an Algorithm

Roberto Erro, MD,[1,2,] Maria Stamelou, MD, PhD,[1,3,4] Christos Ganos, MD,[1,5,6] Matej Skorvanek, MD,[7,8] Vladimir Han, MD,[7,8] Amit Batla, MD, PhD,[1] Kailash P. Bhatia MD, FCRP[1,*]*



One phenotype many genes

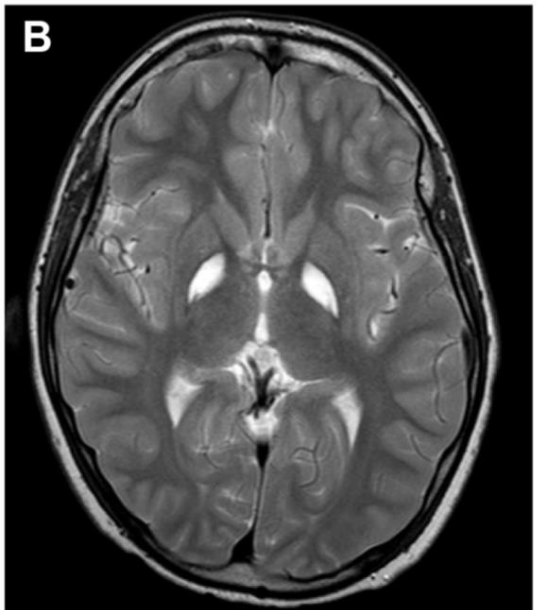


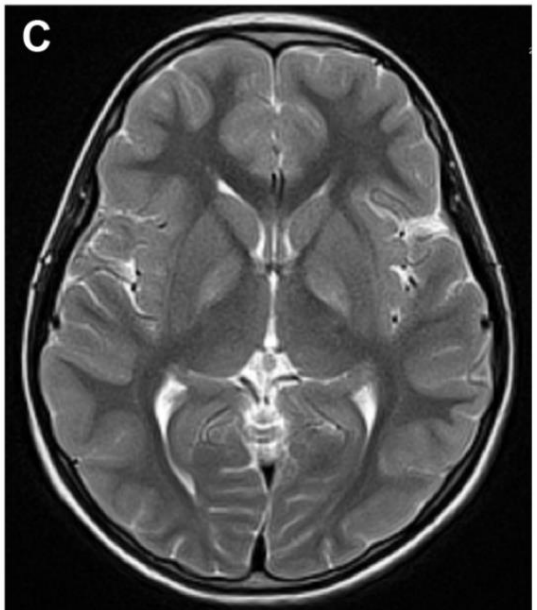
One gene many phenotypes

RESEARCH ARTICLE

Paroxysmal Exercise-Induced Dystonia Within the Phenotypic Spectrum of *ECHS1* Deficiency

Simone Olgiati, MSc,[1] Matej Skorvanek, MD, PhD,[2,3] Marialuisa Quadri, PhD,[1]
Michelle Minneboo, BSc,[1] Josja Graafland, BSc,[1] Guido J. Breedveld, BSc,[1] Ramon Bonte, BSc,[1]
Zeliha Ozgur, BSc,[4] Mirjam C.G.N. van den Hout, PhD,[4] Kees Schoonderwoerd, PhD,[1]
W. Verheijen, PhD,[1] Wilfred F.J. van IJcken, PhD,[4] Hsin Fen Chien, MD, PhD,[5] Egberto Reis Barbosa, MD, PhD,[5]
Hsiu-Chen Chang, BSc,[6] Szu-Chia Lai, MD,[6] Tu-Hsueh Yeh, MD, PhD,[6] Chin-Song Lu, MD,[6]
h-Huei Wu-Chou, PhD,[7] Anneke J.A. Kievit, MD, PhD,[1] Vladimir Han, MD,[2,3] Zuzana Gdovinova, MD, PhD,[2,3]
Robert Jech, MD, PhD,[8] Robert M.W. Hofstra, PhD,[1] George J.G. Ruijter, PhD,[1]
Wim Mandemakers, PhD,[1] and Vincenzo Bonifati, MD, PhD[1]*





Drug-induced dystonia (acute/tardive)

- Neuroleptics (antiemetics)
  - Therapy anticholinergics (Akineton) i.v.
- Antimalarics, late complications of L-dopa, dopamine agonists
- After overdosing - carbamazepine, fenytoin
- No safe neuroleptics (clozapine?), no safe dosis, no safe period of exposure
- Low rate of remission even after discontinuation

Cerebral palsy

- Overdiagnosed + often „escape“ diagnosis!
  - No more examinations needed, no specific treatment“...
- Prenatal a perinatal period!
  - Even perinatal problems may be related to metabolic, mitochondrial or other disorders
- Many patients may have a specifically treatable disorder if their diagnosis is made

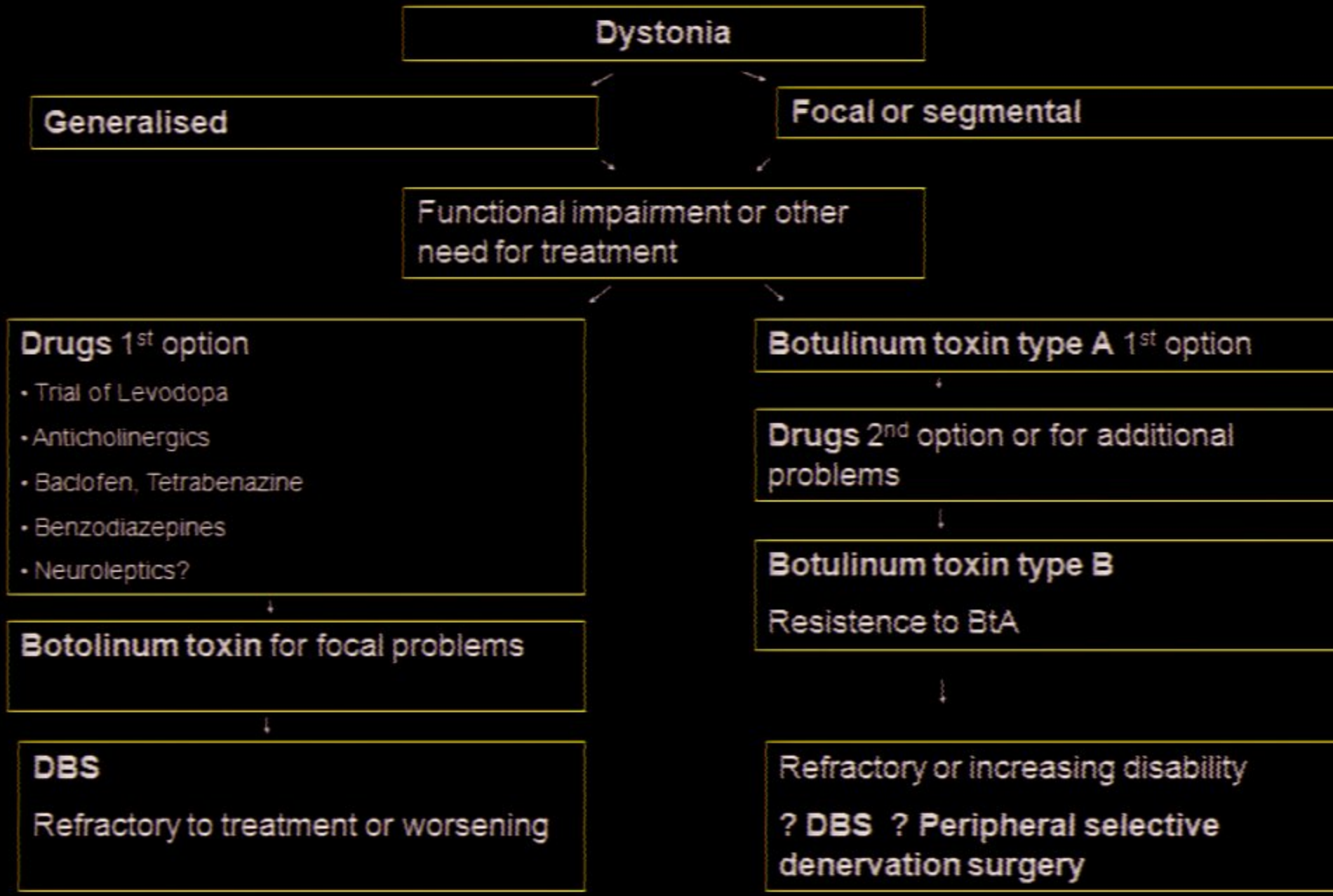
REVIEW

CME

Treatable Inherited Rare Movement Disorders

H. A. Jinnah, MD, PhD,[1*] Alberto Albanese, MD,[2,3] Kailash P. Bhatia, MD,[4] Francisco Cardoso, MD,[5] Gustavo Da Prat, MD,[6,7] Tom J. de Koning, MD, PhD,[8] Alberto J. Espay, MD,[9] Victor Fung, PhD, FRACP,[10]

- **Reduction of toxic products** – Cerebrotendinous xanthomatosis, Dystonia/parkinsonism with manganese accumulation, Gaucher disease, Niemann Pick type C, Wilson disease
- **Dietary interventions** – Abetalipoproteinemia, Cerebral creatine def, GLUT-1 def, Glutaric aciduria type 1, Homocystinuria, Maple syrup urine disease, Methylmalonic aciduria, Phenylketonuria, Propionic acidemia, Pyruvate dehydrogenase complex def, Refsum disease
- **Vitamin supplements** – Abetalipoproteinemia, AADC def, Ataxia with vit E def, Biotin-thiamin responsive basal ganglia disease, Biotinidase def, Cerebral folate def, Cobalamin def, Coenzyme Q10 def, Homocystinuria, Pyruvate dehydrogenase complex def
- **Trigger avoidance** – Alternating hemiplegia of childhood, Biotin-thiamin responsive basal ganglia disease, Episodic ataxia type 2, Glutaric aciduria type 1, Maple syrup urine disease, Methylmalonic aciduria, Paroxysmal kinesigenic / nonkinesigenic dyskinesia, Propionic acidemia, Rapid onset dystonia parkinsonism
- **Specific drugs** – AADC drugs, Dopa-responsive dystonia, Episodic ataia type 2, GLUT-1 defficiency, Molybdenum cofactor defficiency, Paroxysmal kinesigenic dyskinesia


Dystonia
Generalised
Focal or segmental
Functional impairment or other need for treatment
Drugs 1st option
• Trial of Levodopa
• Anticholinergics
• Baclofen, Tetrabenazine
• Benzodiazepines
• Neuroleptics?
Botolinum toxin for focal problems
DBS
Refractory to treatment or worsening
Botulinum toxin type A 1st option
Drugs 2nd option or for additional problems
Botulinum toxin type B
Resistence to BtA
Refractory or increasing disability
? DBS ? Peripheral selective denervation surgery

Botulinum toxin

- First choice and most effective in focal/segmental dystonia
- Chemical muscle denervation
- Therapeutic effect in 2 weeks, lasts usually 3-4 months
- Side effects local, depends on localization and dose – muscle weakness, dysphagia, ptosis, ...
- Possible resistance due to antibodies production, BTX-A can be changed for BTX-B

DBS for dystonia

- Target usually Globus pallidus internus (Gpi DBS)
- Effect usually after a few months
- Best effect in primary generalized dystonia
- DYT1>nonDYT1
- Cervical dystonia refractory to BTX
- Good effect in Myoclonus dystonia, tardive dystonia

Huntingon's disease

- AD inheritance
- Caused by CAG repeat expansion in gene for huntingtin (gene IT15, chromosome 4p)
- Loss of GABAergic striatal neurons
- Prevalence 10/100 000

Manifestation of the disease

- Up to 35 CAG repeats – normal
- 36-39 CAG repeats – variable expression of the disease
- 40 a more CAG repeats – disease always manifested
- Anticipation phenomenon – the higher number of repeats, the sooner the disease starts and the worse is the disease course

Clinical picture + Diagnosis

- Adult form – Combination of chorea, cognitive decline and behavioral changes (onset 30-50 y.)
- Juvenile form – Westphal variant – onset before the age of 21, atypical picture – less chorea, more dystonia, parkinsonism, ataxia, mental retardation, epilepsy
- Late onset variant - approx 4-5% of cases, onset after age of 60

- MRI – atrophy of ncl. caudatus
- Genetic tests

Therapy

- No causal treatment
- Chorea – atypical neuroleptics – risperidone, tiaprid
- Cognitive dysfunction – treatment not effective
- Behavioral problems / psychotic symptoms – clozapine, , quetiapine
- Antidepressants (SSRI), anxiolytics
- Psychotherapy
- Physiotherapy
- Palliative therapy

Wilson's disease

- AR inheritance – ATP7B gene muation, chromosome 13q
- Pathological accumulation of copper
- Prevalence 1-4/100 000

- Hepatal variant – more in childhood
- Neurological/psychiatric variant – more in adulthood – up to 50 years of age

Clinical features

- Hepatal failure
- Any type of movement disorders
  - Especially tremor, dystonia, parkinsonism, ataxia, dysartria
  - Cognitive decline
  - Behavioral problems, psychosis

Diagnosis

- Low blood coeruloplasmin (<200mg/l)
- Increase plasmatic free copper (>1,6umol/l)
- Increased urine copper levels (24h)
- Liver biopsy
- Kayser-Fleischer rings
- Brain MRI (nonspecific)
  - „Giant panda sign“
  - Hyperintensive basal ganglia changes
  - Brain atrophy

Therapy

- Penicilamine (necessary to administrate with pyridoxine)
- Zinc salts – slower effect onset, but less side effects
- Liver transplant

- Therapy lifelong, can’t be interrupted!!!!

Hotel DoubleTree by Hilton, Kosice, Slovakia

17-19 May 2018

www.expy-ke.sk