Extrapyramidal (Movement) disorders

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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.
<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Conditions</th>
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<tbody>
<tr>
<td><strong>Idiopathic Parkinson’s disease (80%)</strong></td>
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<tr>
<td><strong>Symptomatic secondary parkinsonism (10%)</strong></td>
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<tr>
<td>• Drug-induced</td>
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<td>• Toxic – M.Wilson, Mn, CO, MPTP</td>
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<td>• Traumatic</td>
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<td>• Vascular</td>
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<tr>
<td>• Parkinsonian syndrome in normal-pressure hydrocephalus</td>
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<tr>
<td><strong>Neurodegenerative parkinsonian syndromes (10%)</strong></td>
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<tr>
<td>• Multiple system atrophy</td>
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<tr>
<td>• Progressive supranuclear palsy</td>
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<tr>
<td>• Corticobasal degeneration</td>
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<tr>
<td>• Dementia with Lewy bodies</td>
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### Pathology of neurodegenerative parkinsonism

<table>
<thead>
<tr>
<th>Synucleinopathies</th>
<th>Tauopathies</th>
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<tbody>
<tr>
<td>• Parkinson’s disease</td>
<td>• Progressive supranuclear palsy</td>
</tr>
<tr>
<td>• Parkinson’s disease with dementia</td>
<td>• Corticobasal degeneration</td>
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<tr>
<td>• Lewy body dementia</td>
<td>• Frontotemporal lobar degeneration</td>
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<tr>
<td>• Multiple system atrophy</td>
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</table>
Parkinson’s disease - definition

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

• Loss of nigrostriatal neurons and presence of intracellular 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
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 α-synuclein spreading?

Native α-syn (random coil) → Molecular chaperones → Misfolded proteins → Oligomers (β-pleated sheet) → Amyloid fibrils (β-pleated sheet) → Phagosomes and lysosomes → Proteasome → Autophagy → Peptides → Oxidative stress → Protein sequestration → Disruption of axonal transport → Synaptic dysfunction → Inhibition of UPS → Mitochondrial dysfunction

Levy neurite → Levy body → Transmission

Irwin et al., Nat Rev Neurosci 2013
Spreading of α-synuclein

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

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

Proof of a-syn presence in the enteric nervous system

Skorvanek et al. Mov Disord 2018
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, FRCP,⁵ Wolfgang Oertel, MD,⁶ José Obeso, MD, PhD,⁷ Kenneth Marek, MD,⁸ Irene Litvan, MD,⁹ Anthony E. Lang, OC, MD, FRCP,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 Deuschi, MD¹⁸

• 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\textsuperscript{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, graphesthesis, 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 the 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—aorthostatic 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)

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

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Sensory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central fatigue (maybe related to dysautonomia)</td>
<td>Pain</td>
</tr>
<tr>
<td>Peripheral fatigue</td>
<td>Olfactory disturbance</td>
</tr>
<tr>
<td></td>
<td>Hyposmia</td>
</tr>
<tr>
<td></td>
<td>Functional anosmia</td>
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<tr>
<td></td>
<td>Visual disturbance (blurred vision, diplopia), impaired contrast-sensitivity</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Autonomic dysfunction</th>
<th>Gastrointestinal symptoms</th>
</tr>
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<tbody>
<tr>
<td>Bladder urgency, frequency, nocturia</td>
<td>Dribbling of saliva</td>
</tr>
<tr>
<td>Sexual dysfunction (may be drug-induced)</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Sweating abnormalities (hyperhidrosis)</td>
<td>Ageusia</td>
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<tr>
<td>Orthostatic hypotension</td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Nausea</td>
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<tr>
<td></td>
<td>Vomiting</td>
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<tr>
<td></td>
<td>Reflux</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence</td>
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<tr>
<td><strong>Dopaminergic drug-induced behavioural NMS</strong></td>
<td><strong>Dopaminergic drug-induced “other” NMS</strong></td>
</tr>
<tr>
<td>Hallucinations, psychosis, delusions</td>
<td>Ankle swelling</td>
</tr>
<tr>
<td>Dopamine dysregulation syndrome (usually linked to levodopa intake)</td>
<td>Dyspnoea (maybe linked to ergot dopamine agonist related cardiac/respiratory failure)</td>
</tr>
<tr>
<td>Impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating)</td>
<td>Subcutaneous nodules (apomorphine)</td>
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<tr>
<td></td>
<td>Erythematous rash (rotigotine patch)</td>
</tr>
<tr>
<td><strong>Other symptoms</strong></td>
<td><strong>Non-motor fluctuations</strong></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Dysautonomic</td>
</tr>
<tr>
<td>Weight gain (could be related to impulse control disorders)</td>
<td>Cognitive/Psychiatric</td>
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<tr>
<td></td>
<td>Sensory/Pain</td>
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<td></td>
<td>Visual blurring</td>
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</table>

Evolution of NMS

Medication effect
- ICDs
- Sleep attacks
- Nonmotor fluctuations
- DDS, punding
- EDS
- Visual hallucinations
- RBD
- Constipation
- Urinary urgency
- Erectile dysfunction
- Depression
- Hyposmia
- Pain
- PIGD
- Dementia

Intrinsic to PD

Relative contribution of dopaminergic MEDICATION vs. DISEASE

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 treatment
- **Wearing-off**: short off periods
- **Wearing-off with dyskinesias**: Predictable peak-of-dose dyskinesias
- **On-off fluctuations**: Unpredictable fluctuations
- **Very narrow therapeutic window**

**Therapeutic window**

- ~0-4 years
- ~4-7 years
- ~7-10 years
- ~>10 years

- **Normal mobility**
- **Parkinsonism**
- **Dyskinesias**
Rational pharmacotherapy of early PD

Motor symptoms

- No functional disability

- Functional disability

Dopamine agonists

- Symptomatically insufficient

Add-on Levodopa

Rasagiline

Amantadine monotherapy
COMT inhibitors monotherapy
Rational pharmacotherapy of early PD

Motor symptoms

- No functional disability: Rasagiline
- Functional disability: Dopamine agonists

Dopamine agonists

- Symptomatically insufficient: Add-on Levodopa
- Old+ demented: Anticholinergics

Add-on Levodopa

Tremor
PD disease course on treatment

Early stage
Good response to dopaminergic treatment

Wearing-off
Short off periods

Wearing-off with dyskinesias

On-off fluctuations
Unpredictable fluctuations

Predictable peak-of-dose dyskinesias

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

- **Early stage**: Good response to dopaminergic treatment
- **Wearing-off**: Short off periods
- **Wearing-off with dyskinesias**: Predictable peak-of-dose dyskinesias
- **On-off fluctuations**: Unpredictable fluctuations
- **Very narrow therapeutic window**

**Therapeutic window**
Peak-of-dose dyskinesias - strategy

1. Administration of levodopa more frequently and in lower doses

2. Add-on amantadine
PD disease course on treatment

*Early stage*:
- Good response to dopaminergic treatment

*Wearing-off*:
- Short off periods

*Wearing-off with dyskinesias*:
- Predictable peak-of-dose dyskinesias

*On-off fluctuations*:
- Unpredictable fluctuations
- Very narrow therapeutic window

**Therapeutic window**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>0-4</th>
<th>4-7</th>
<th>7-10</th>
<th>&gt;10</th>
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<tbody>
<tr>
<td>Normal mobility</td>
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<tr>
<td>Parkinsonism</td>
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<tr>
<td>Dyskinesias</td>
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</table>
• 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
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
- Excellent response in L-dopa test
- Good social background

- Presence of levodopa-resistant symptoms
- Preoperative cognitive defect
- Comorbidities (DM, cardiac failure, stroke)
- Dopamine dysregulation syndrome
- Balance problems, dysarthria
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?
Therapeutic decision

- Fluctuations
- Social background
- Single dose effect
- Nonmotor symptoms
- Age
- Expectations
- Comorbidity
Essential tremor

• only tremor!!! (mostly on action)
• often positive family history
• usually excellent 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 dysarthria
  - 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

<table>
<thead>
<tr>
<th>Sporadic progressive disorder with onset after the age of 30</th>
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<tbody>
<tr>
<td>Presence of autonomic dysfunction</td>
</tr>
<tr>
<td>• urine retention/erectile dysfunction</td>
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<tr>
<td>• orthostatic hypotension – decrement of &gt;30/15 torr</td>
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<tr>
<td>AND</td>
</tr>
<tr>
<td>Parkinsonism</td>
</tr>
<tr>
<td>OR</td>
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<tr>
<td>Cerebellar syndrome</td>
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</table>

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
Progressive supranuclear palsy (PSP)

- progressive sporadic neurodegenerative disorder
- Presence of parkinsonism, supranuclear vertical gaze 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

<table>
<thead>
<tr>
<th>Cognitive decline</th>
<th>Speech disorder</th>
</tr>
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<tbody>
<tr>
<td>• Executive dysfunction</td>
<td>• Can be independent from cognitive decline</td>
</tr>
<tr>
<td>• Visuo-spatial dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Movement disorders</strong></td>
<td><strong>Other cortical abnormalities</strong></td>
</tr>
<tr>
<td>Asymmetric parkinsonism</td>
<td>• Apraxia</td>
</tr>
<tr>
<td>Asymetrická dystonia</td>
<td>• Alien limb phenomenon</td>
</tr>
<tr>
<td>Tremor</td>
<td>• Cortical sensitivity dysfunction</td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
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<tr>
<td>Gait disorder with early falls</td>
<td></td>
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<tr>
<td><strong>Insufficient levodopa response</strong></td>
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</table>
Therapy of atypical parkinsonism

Parkinsonism
• 1. Levodopa!!!!

Dystonia – if focal and bothersome
• Botulotoxin

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

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 classification 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
- Phoniatic exam – normal
- Abdominal USG – normal
- Muscle enzymes – normal
- Genetic exam - „normal“
  - karyotype
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 attacks
• Non-epileptic
The Clinical Syndrome of Paroxysmal Exercise-Induced Dystonia: Diagnostic Outcomes and an Algorithm

Roberto Erro, MD, Maria Stamou, MD, PhD, Christos Ganos, MD, Matej Skorvanek, MD, Vladimir Han, MD, Amit Batla, MD, PhD, Kailash P. Bhatia MD, FCRP

PED → MRI
- Normal
- Abnormal → Symptomatic PED

Onset Age
- Childhood
- Early Adulthood

CSF investigations *
- Low CSF/serum glucose ratio or low CSF glucose value (<10th percentile) with normal lactate
- Low BH4, HVA, HIAA

DRD
- (requires testing for the GCH1 gene)
- GLUT-1 (requires testing for the SLC2A1 gene)
- Ketogenic diet

DaT-Scan
- Normal
- Abnormal → PD
  (further genetic testing for early onset PD genes may be pursued)
  Anti-parkinsonian drugs
  (dopaminergic or anticholinergic drugs may be tried according to the clinical judgment)

DRD
- Empirical management
  (Levodopa, Botulinum toxin, Clonazepam, AEs may be tried)
- Levodopa

Levodopa
One phenotype many genes

DYT6 (THAP1 gene)

DYT24 (ANO3 gene)

Iné gény
One gene many phenotypes

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

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Robert Jech, MD, PhD,8 Robert M.W. Hofstra, PhD,3 George J.G. Frijters, PhD,1
Wim Mandemakers, PhD,1 and Vincenzo Bonifati, MD, PhD1
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
Treatable Inherited Rare Movement Disorders

H. A. Jinnah, MD, PhD, Alberto Albanese, MD, Kailash P. Bhatia, MD, Francisco Cardoso, MD, Gustavo Da Prat, MD, Tom J. de Koning, MD, PhD, Alberto J. Espay, MD, Victor Fung, PhD, FRACP

• **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 deficiency, Molybdenum cofactor deficiency, 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?

Botulinum toxin type A 1st option

Drugs 2nd option or for additional problems

Botulinum toxin type B
Resistance to BtA

DBS
Refractory to treatment or worsening

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
Huntington’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 mutation, 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!!!!
Kosice Course of Movement Disorders

Hotel DoubleTree by Hilton, Kosice, Slovakia
17-19 May 2018

www.expy-ke.sk