“Beyond Atypical-atypical Parkinsonisms”

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Dopamine receptors interactions
Young-onset PD
Trophic effects of Levodopa
Sleep and PD
Dyskinesia molecular underpinnings
When a patient comes to see you, he is under no obligation to have a simple disease just to please you.

Let someone say a doctor that he really knows his physiology or anatomy, that he dynamic-these are not real compliments, but *if you say that he is an observer, one who knows how to see*, this is perhaps the greatest compliment one can make.

Theory is good; but it doesn't prevent things from existing.
• Every patient we see with Parkinsonism poses a diagnostic challenge

• Not every Parkinsonism is Parkinson’s disease

• Not every case within the spectrum of Parkinsonism presents itself as parkinsonism
• In 2013 Stamelou et al published a paper with the suggestive title “Atypical-atypical Parkinsonism”

• It raised the question as to what is “typical” or “atypical” in that “Pandora’s box” we call parkinsonism!!
Due to the lack of specific biomarkers, phenomenological diagnosis of parkinsonism is done mostly through pattern recognition and diagnostic criteria are often based on recognition of these distinctive patterns and supportive features.

In my practice I have adopted the following personal classification to systematically approach these cases and I would like to share it with you.
# What is Typical or Atypical Parkinsonism?

<table>
<thead>
<tr>
<th>“Typical Parkinsonism”</th>
<th>IPD (classic presentation, tremor dominant or akinetic-rigid dominant, asymmetry, no atypical features, supportive criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Atypical-typical Parkinsonism” (Typical Parkinsonism of atypical presentation)</td>
<td>Isolated unilateral tremor, postural instability-gait disturbance (PIGD)</td>
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<tr>
<td>“Typical atypical Parkinsonism”</td>
<td>MSA, PSP, CBD</td>
</tr>
<tr>
<td>“Atypical-typical-atypical Parkinsonism” (Typical atypical Parkinsonism of atypical presentation)</td>
<td>Different phenotypes and variable clinical course of MSA, PSP, and CBD</td>
</tr>
<tr>
<td>“Atypical-atypical Parkinsonism” (Everything not included in the other categories. They may present with features of Typical Parkinsonism, mimic Typical-atypicals or have complex phenotypes)</td>
<td>SCA, FXTAS, Kufor Rakeb, Perry syndrome, Gaucher, NPC, PRNP, NBIA, PPND, HSP,CTX, Mitochondrial, Vascular pseudoparkinsonism, lower body parkinsonism, NPH, monogenic PD with atypical phenotypes, autoimmune, etc.</td>
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</table>
Phenomenology Caveats

- Typical or Typical-atypical phenotypes do not preclude the possibility that they correspond to Atypical-atypicals.

- Careful history taking, both personal and family. Carefully review existence of systemic involvement.

- Comprehensive neurologic examination looking for additional or atypical features.
• Remember the 5 year rule:

• Patients may initially appear to be typical but can change during the course of the disease and point you in the direction of either an Atypical-typical-atypical or an Atypical-atypical
Atypical-typical Parkinsonism

**Isolated tremor:** Unilateral, asymmetric, either rest, postural or mixed
- Out of 36 patients with abnormal 123I-FPCIT SPECT 64% progressed to PD

**(PIGD)** Postural Instability Gait Disturbance phenotype of PD
- Predominantly axial involvement (more a state marker than a trait). Originally reported as *Lower body parkinsonism*

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Atypical Parkinsonism

• **Typical (most frequent):**
  - Multiple System Atrophy (MSA)
  - Progressive Supranuclear Palsy (PSP)
  - Corticobasal Degeneration (CBD/CBS)

• **Atypical:** Keep in mind the existence of atypical presentations of “Typical-atypical Parkinsonisms”
## MSA: Clinical variants (atypical)

- **MSA-P (Predominant Parkinsonism)**
- **MSA-C (Predominant Cerebellar)**

<table>
<thead>
<tr>
<th>Minimal change MSA (MSA-MC)</th>
<th>Benign MSA (MSA-B)</th>
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<tbody>
<tr>
<td>Earlier onset (38 vs 57.6 years)</td>
<td>MSA-P in all cases</td>
</tr>
<tr>
<td>More rapid course (clinical milestones at 3 years)</td>
<td>Development of dysautonomia up to 11 years after onset of Parkinsonism</td>
</tr>
<tr>
<td>Severe respiratory dysfunction</td>
<td>On average 9 years from onset to the development of antecollis, laryngeal stridor and dysphagia</td>
</tr>
<tr>
<td>Early orthostatic hypotension</td>
<td>Limited response to levodopa, but all with dyskinesia</td>
</tr>
<tr>
<td>Sudden death frequent</td>
<td></td>
</tr>
<tr>
<td>Greater degree of GCI in SN and Caudate</td>
<td></td>
</tr>
</tbody>
</table>

*Ling et al 2015, Petrovic et al 2012*
PSP: Clinical Variants (atypical)

- **PSP-P**: asymmetric parkinsonism with rest tremor and response to levodopa
- **PSP-CBS**: progressive asymmetric dystonia, apraxia, alien hand and cortical sensory deficit
- **PSP-PAFG**: global akinesia and gait disturbances (start- and turn-hesitation, FOG), writing arrests and speech arrest
- **PSP-PNFA**: prominent language disorder, language apraxia, progressive non-fluent aphasia

*Other atypical variants: FTD-like, ALS-like, MSA-like, OCD or psychosis, pure oculomotor PSP-OM, postural instability or ataxia PSP-I/PSP-A*

Corticobasal Degeneration (CBD) (Atypical)

• Multiple phenotypes:
  – Corticobasal Syndrome (CBS)
  – Frontal-behavioral-spatial Syndrome (FBS)
  – Non-fluent/agrammatic variant of primary progressive aphasia (nfaPPA)
  – PSP-like Syndrome (PSPS)
  – Posterior Cortical Atrophy (PCA)
  – Dementia of the Alzheimer type (DAT)

In view of its great clinical variability and multiple etiologies presenting with CBS the possibility of a positive ante-mortem diagnosis varies from 25 to 56%
Corticobasal syndrome (CBS)

• Can be seen in:
  – Progressive supranuclear palsy
  – Alzheimer’s disease
  – Pick’s disease
  – FTLD-TDB (frontotemporal lobar degeneration with TAR DNA binding protein 43 [TDP-43]-immunoreactive inclusions or progranulin mutations [PGRN] or MAPT mutations)
  – Stroke (“the great pretender”)
  – CJD

Boeve 2011, Ouchi et al 2014
“Atypical Parkinsonism: clues for its recognition”

• When do we suspect we are faced with an atypical parkinsonism? (Typical-atypical, Atypical-typical atypical or Atypical-atypical)
  – By the age and mode of onset
  – By the presence of family history
  – By the clinical course
  – By the clinical phenomenology
  – By the imaging findings
  – By the pharmacological response to levodopa

_Suspicious cases may require specific lab determinations (e.g. urinary copper and ceruloplasmin in Wilson’s disease, cholesterol to cholestanol ratio in CTX)_
“Atypical Parkinsonism: clues for its recognition”

• When do we suspect we are faced with an atypical parkinsonism?:
  – By the age and mode of onset
  – By the presence of family history
  – By the clinical course
  – By the clinical phenomenology
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  – By the pharmacological response to levodopa
“Atypical Parkinsonism: clues for its recognition”

Age of onset

**Young or very young**
- Genetic Parkinsonism
  - Parkin, DJ-1, PINK-1
  - Kufor-Rakeb (PARK 9 [ATP13A2]), PLAN (PARK 14 [PLA2G6])
  - Catecholamine Metabolism Disorders (GTPCH1, TH, DDC, SPR)
  - RDP (DYT12 [ATP1A3])
  - PARK 15 (FBXO7), SPG11 (spatacsin)
- Wilson’s disease
- Niemann-Pick type C
- Huntington’s disease

**Advanced age**
- Isolated senile bradykinesia
- Frontal dementia
- Vascular Pseudoparkinsonism
- NPH

Age of onset
Atypical Parkinsonism: clues for its recognition

Mode of onset

- Sudden onset
  - Stroke
- Instability and falls
  - DLB, PSP, MSA
- Psychiatric or cognitive disorders
  - FTD, HD, WD, DLB
- Dysarthria
  - MSA

- Limb apraxia
  - CBS
- Hallucinations
  - DLB
- Dysautonomia
  - MSA, DLB
When do we suspect we are faced with an atypical parkinsonism?:

- By the age and mode of onset
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</table>

### Dominant family history
- FTD
- FTD/ALS overlap
- Perry Syndrome
- SCA’s (2,3)
- Genetic CJD
- AD

### No family history or recessive
- Gaucher’s disease
- Niemann-Pick C
- Mitochondrial
- Kufor-Rakeb
- Cerebrotendinous Xanthomatosis
- FXTAS
- HSP

*Stamelou et al, 2013*
When do we suspect we are faced with an atypical parkinsonism?:

- By the age and mode of onset
- By the presence of family history
- By the clinical course
- By the clinical phenomenology
- By the imaging findings
- By the pharmacological response to levodopa
“Atypical Parkinsonism: clues for its recognition”

• Stepwise course
  – Vascular Pseudoparkinsonism

• Rapid course to maximum disability in a few years (wheelchair sign)
  – MSA
  – PSP
  – RDP
  – Most of the “atypical atypicals”

• Dementia within one year from onset
  – DLB
When do we suspect we are faced with an atypical parkinsonism?:

- By the age and mode of onset
- By the presence of family history
- By the clinical course
- By the clinical phenomenology
- By the imaging findings
- By the pharmacological response to levodopa
### Clinical Phenomenology

<table>
<thead>
<tr>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor disturbances (supranuclear gaze palsy)</td>
<td>PSP, NPC, KRS, CBD</td>
</tr>
<tr>
<td>Cerebellar Syndrome (ataxia, dysarthria)</td>
<td>MSA, FXTAS, SCA’s</td>
</tr>
<tr>
<td>Pseudobulbar Syndrome</td>
<td>PSP</td>
</tr>
<tr>
<td>Postural disturbances</td>
<td>Antecollis (MSA), Retrocollis (PSP)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>RDP, PLAN, PARK 15, DRD, CBS, FTD</td>
</tr>
<tr>
<td>Alien hand syndrome, apraxia, agnosia, aphsia, palilalia, echolalia</td>
<td>CBS, PSP, FTD</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>CBS, KRS, MSA, Mitochondrial</td>
</tr>
<tr>
<td>Incomplete Parkinsonism (pure akinesia, isolated unilateral tremor, lower body parkinsonism)</td>
<td>PSP, Dystonic tremor, VP</td>
</tr>
<tr>
<td>Depression, weight loss, central apneas</td>
<td>Perry syndrome</td>
</tr>
<tr>
<td>Piramidalism, spasticity</td>
<td>Pallidopyramidal syndrome (KRS, PARK 14 and 15, SPG 11), VP</td>
</tr>
<tr>
<td>Oculogyric crises</td>
<td>DRD (SPRD, DDCD, THD)</td>
</tr>
<tr>
<td>Cognitive deterioration, dementia</td>
<td>FTD, CBS, DLB, HD, PSP, KRS, FXTAS, VP</td>
</tr>
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</table>
Limitations of phenomenology based diagnosis

• Some cases of Atypical-typical-Atypical Parkinsonisms, and likewise, some cases of Atypical-Atypical Parkinsonisms may present with clinical features indistinguishable from Typical Parkinsonism (IPD)

• Moreover, response to levodopa may be present
“Atypical Parkinsonism: clues for its recognition”

- When do we suspect we are faced with an atypical parkinsonism?:
  - By the age and mode of onset
  - By the presence of family history
  - By the clinical course
  - By the clinical phenomenology
  - By the imaging findings
  - By the pharmacological response to levodopa
Neuroimaging in MSA

MRI, T2 (axial): Pontine and cerebellar atrophy

MRI, T2 (sagital): Pontine and cerebellar atrophy

MRI, Flair: Increased signal in the brainstem (medial raphe and pontine transversal fibers), “hot cross bun sign”

MRI, Flair: Bilateral posterolateral putaminal hypointensity

Midbrain sonography
Echogenicity corresponding to SN <0.2 cm²

18 FDG-PET
A. Putaminal hypometabolism
B. Cerebellar hypometabolism

SPM t-map
‘voxel-based’ statistical parametric mapping

MIBG scintigraphy
Cardiac sympathetic innervation

Own images, Goldstein 2003, Walter 2003, Kwon 2007, Brajkovic 2017
Neuroimaging in PSP

- Humming bird sign
- Interpeduncular cistern hyperintensity
- Periaqueductal hyperintensity
- Hypointensity and putaminal atrophy


“Morning glory sign”

FDG-PET: Dorsolateral and medial frontal hypometabolism

Hypometabolism in the frontal cortical region (medial, dorsolateral), midbrain and both caudate nuclei (FDG-PET and SPM-t map)

Midbrain to pons ratio

A midbrain measurement of <9.35 mm and ratio of 0.52 had 100% specificity for PSP*
Automated brainstem volumetry

Sjostrom et al 2020
Neuroimaging in CBS

T1 MRI
Asymmetric frontoparietal atrophy

CBD
Control

Diffusion tensor MR imaging tractography
Asymmetric corticospinal atrophy

Asymmetric hypometabolism in the left parietal and frontal cortices and basal ganglia contralateral to the clinically more affected side
FDG-PET and SPM-t map

Neuroimaging in NBIA

BPAN

PARKINSONISM IN NBIA (undetermined)

PLAN

KUFOR-RAKEB

Fekete, 2012; Stige et al, 2018
Neuroimaging in Wilson’s disease
Neuroimaging in FRXTAS (MCP and subortical hyperintensity). Only 60 to 80% of FRXTAS patients present typical imaging findings.

Berry-Kravis et al., 2007; Horvath & Burkhard, 2007; Nitrini et al., 2010
Limitations of neuroimaging based diagnosis

- Suggestive imaging findings may not be present at all
- When present, they may become evident late in the course of the disease and not help in early diagnosis
- Not always highly sensitive or specific
When do we suspect we are faced with an atypical parkinsonism?:

- By the age and mode of onset
- By the presence of family history
- By the clinical course
- By the clinical phenomenology
- By the imaging findings
- By the pharmacological response to levodopa
“Atypical Parkinsonism: clues for its recognition”

- Initial therapeutic failure
  - MSA, PSP, CBS (with exceptions)
  - “Atypical” atypicals (with exceptions)
- Rapid loss of therapeutic response
  - MSA, PSP
  - “Atypical” atypicals
- Great response to levodopa
  - DRD, Genetic Juvenile Parkinsonism (e.g. Parkin)
A negative response to high doses of levodopa, **having ruled out malabsorption**, is an exclusionary criteria in the diagnosis of PD


Published series (1983) of 44 patients clinically diagnosed as PD, 18% less than 25% initial improvement and 40% considered poor responders after 3 years


In Hughes et al., initial response to levodopa was “null or poor ” in 6%, “moderate” in 17%, “good” in 53%, and “excellent” in 24%


30% of false negatives with a levodopa test

Flow chart for the diagnosis of Parkinsonism

Comprehensive history taking and full neurological exam are critical

Typical exam

- IPD (5 year rule)*

Atypical exam

- Atypical presentation of IPD (Atypical-Typical Parkinsonism)
- Typical presentation of Atypical Parkinsonism ( Typical-Atypical Parkinsonism)
- Atypical presentation of Typical Atypical Parkinsonism ( Atypical-Typical-Atypical Parkinsonism)
- Atypical-atypical Parkinsonism

Include:
- Age and mode of onset
- Family history
- Clinical course
- Clinical features
- Imaging findings
- Response to levodopa

* Important caveat: Some AAP and ATAP may be phenotypically indistinguishable from IPD
Thank you!!!