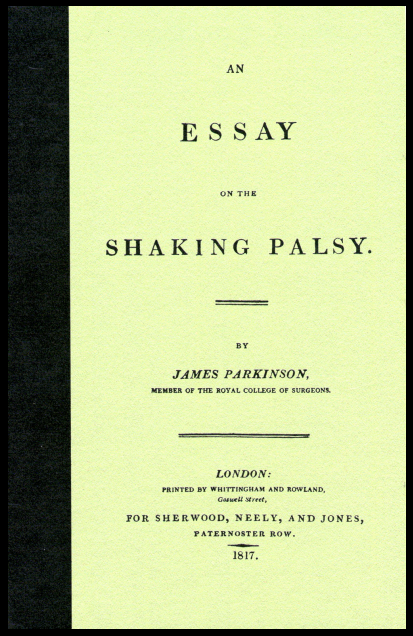
The evolving differential diagnosis of Parkinson's disease


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.

Richard J Davenport
Edinburgh

The problem

- 74 yr old male
  - Shakey, mainly R hand
  - ?mother had a shake
  - Not much else
- Is this parkinsonism?
  - If yes…..is it PD or something else?
  - If no……what is it?

1817

- James Parkinson
  - "*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the sense and intellects being uninjured*."

1817

- James Parkinson
  - "*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the sense and intellects being uninjured*."
  - Chapter 3: Shaking Palsy distinguished from other diseases with which it may be confounded

The clinical dilemma

- JP described a clinical syndrome….
- …now defined pathologically…
- ……..but we need to diagnose in life
- PD is…
  - ....progressive clinical syndrome incorporating motor and non-motor symptoms/signs, some responding well to LD

Journal of Neurology, Neurosurgery, and Psychiatry 1992;55:181–184

Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases

Andrew J Hughes, Susan E Daniel, Linda Kilford, Andrew J Lees

- 100 patients prospectively diagnosed
  - "*by a group of neurologists*"
  - 76 confirmed pathologically
  - 24 false positives
    - PSP, MSA, AD, vascular disease…

VIEWS & REVIEWS

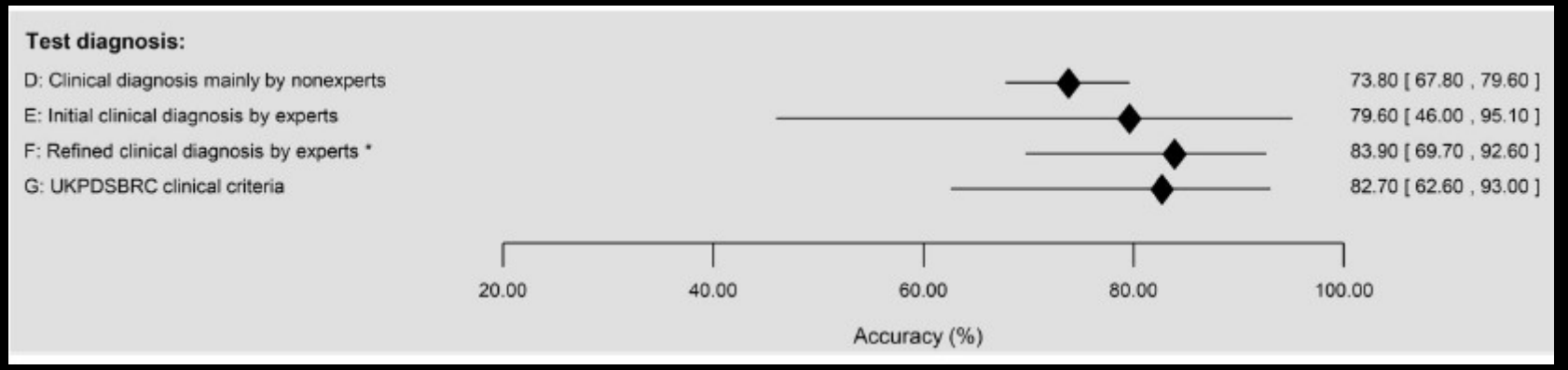
Accuracy of clinical diagnosis of Parkinson disease

A systematic review and meta-analysis

Giovanni Rizzo, MD

ABSTRACT

- 11 studies used pathology as GS



Neurology® 2016;86:566-576

What did we miss?

- False positives
  - ET, PSP, V encephalopathy, MSA, DLB, drug induced
  - MSA, PSP, DLB, AD, VaE
- False negatives
  - Park in dementia, nonpark tremor, drug induced, MSA, DLB
  - Undetermined parkinsonism, MSA, PSP, VaE

What is PD anyway?

- *…….call into question current concepts of PD as a single distinct entity (1992)*
- *PD increasingly conceptualised as several different diseases within a phenotypic spectrum (2017)*
- Pathology
  - Crossover with AD/vascular pathology
  - Genetic forms of PD without synuclein deposition

Diagnostic criteria

- 1988: UK BB Criteria (*Gibb & Lees*)
- 1992: Calne, Snow & Lee
- 1999: Gelb, Oliver & Gilman
- 2003: Litvan et al

UK Brain Bank criteria

- Step 1: bradykinesia plus
  - Rigidity
  - 4-6 Hz Rest tremor
  - Postural instability
- Step 2
  - Exclusion criteria
- Step 3
  - Supportive criteria

1. Early stage disease
2. Absence of evidence for subtypes
3. DLB and PD not mutually exclusive
4. Clinicogenetic PD

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]

Movement Disorders, Vol. 30, No. 12, 2015

MDS Criteria 2015

1. Identify parkinsonism
   - Bradykinesia +
     - Rest tremor, rigidity, or both

Bradykinesia?

- Slowness of movement AND
- Decrement in amplitude or speed
  - Finger tapping
  - Hand movements
  - Pronation-supination
  - Toe or foot tapping

MDS Criteria 2015

1. Identify parkinsonism
   - Bradykinesia +
     - Rest tremor, rigidity, or both
2. PD as the cause of parkinsonism
   - Supportive criteria
   - Absolute exclusion criteria
   - Red flags

Supportive criteria

1. Dramatic response to DA therapy
2. LD induced dyskinesias
3. Rest tremor of a limb
4. Olfactory loss or
   Abnormal cardiac MIBG scintigraphy

Absolute exclusions

- Signs
  - Cerebellar signs
  - Downgaze supranuclear palsy
  - Restricted to legs >3 years
  - Cortical sensory loss, apraxia or aphasia
- Drugs
  - Known to induce parkinsonism
  - No response to LD (>600mg/day)
- Alternative diagnosis
  - *bv*FTD or PPA within 5 years
  - Other diagnosis to account for parkinsonism
- Investigations
  - Normal functional imaging of pre-synaptic DA system

Red flags

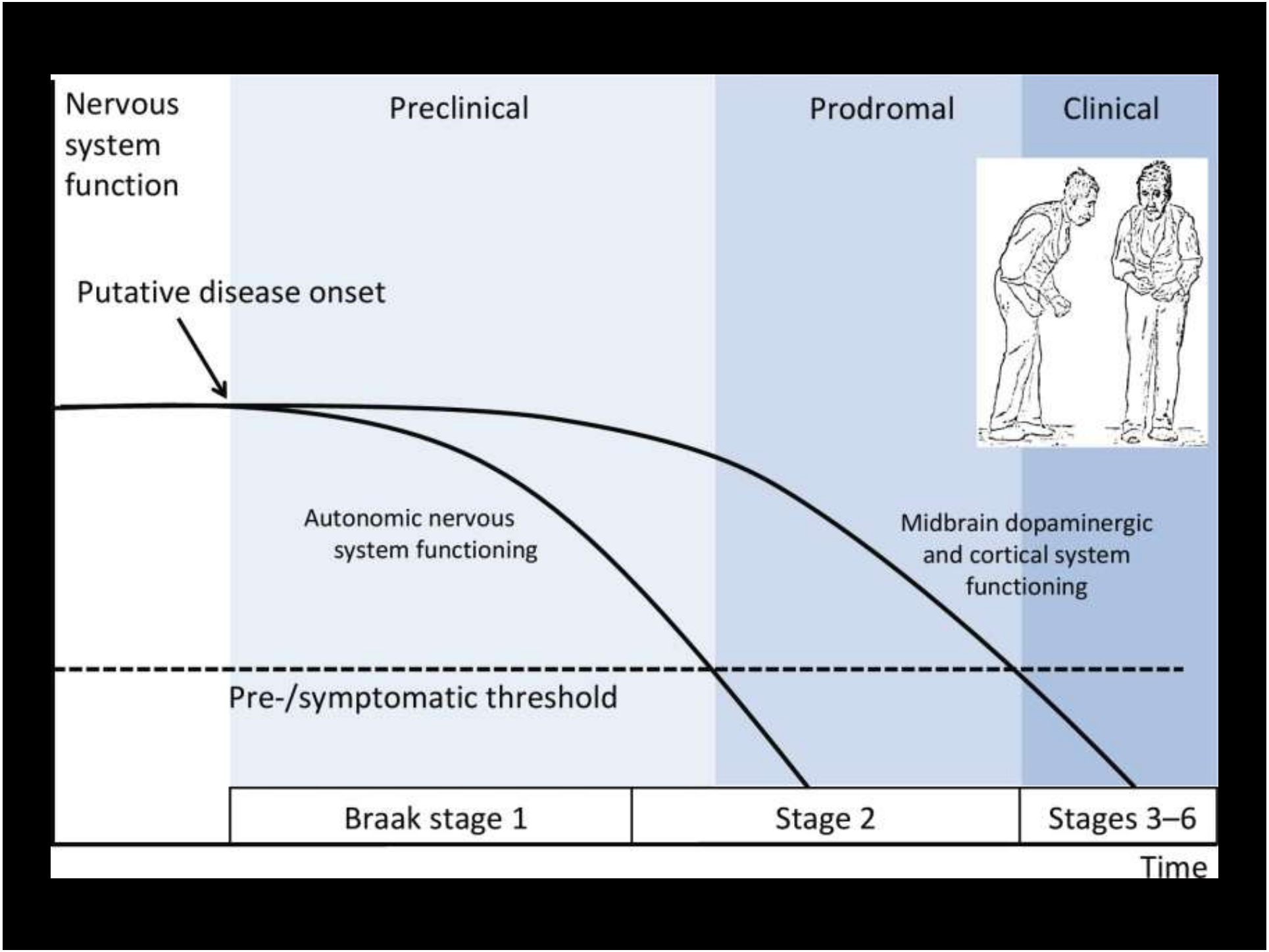
- Symptoms
  - Recurrent falls (3 years)
  - Early bulbar/autonomic (5 years)
  - Absence of common NMS (5 years)
  - Dystonic anterocollis/hand/feet contractures (10 years)
  - Inspiratory respiratory dysfunction
- Signs
  - Unexplained UMN
  - Bilateral symmetrical parkinsonism
- Progression
  - Needing wheelchair within 5 years
  - No progression over 5 years

Diagnostic groups

1. Clinically established PD
   - Absence of absolute exclusion criteria
   - At least 2 supportive criteria
   - No red flags
2. Clinically probable PD
   - Absence of absolute exclusion criteria
   - Supportive criteria counterbalance red flags (no more than 2)

Early stage disease?

- Preclinical
- Prodromal
- Clinical


Nervous system function
Preclinical
Prodromal
Clinical
Putative disease onset
Autonomic nervous system functioning
Midbrain dopaminergic and cortical system functioning
Pre-/symptomatic threshold
Braak stage 1
Stage 2
Stages 3–6
Time

Prediagnostic presentations of Parkinson's disease in primary care: a case-control study

Anette Schrag, Laura Horsfall, Kate Walters, Alastair Noyce, Irene Petersen

Summary

Background Parkinson's disease has an insidious onset and is diagnosed when typical motor features occur. Several motor and non-motor features can occur before diagnosis, early in the disease process. We aimed to assess the association between first presentation of several prediagnostic features in primary care and a subsequent diagnosis of Parkinson's disease, and to chart the timeline of these first presentations before diagnosis.

Methods We identified individuals with a first diagnosis of Parkinson's disease and those without Parkinson's disease

Lancet Neurol 2014; 14: 57–64
Published Online
November 27, 2014
http://dx.doi.org/10.1016/S1474-4422(14)70287-X

See Comment page 27

- The Health Improvement Network (THIN) UK
  - 11M longitudinal health records
  - PwPD (8166) and controls (46 755)

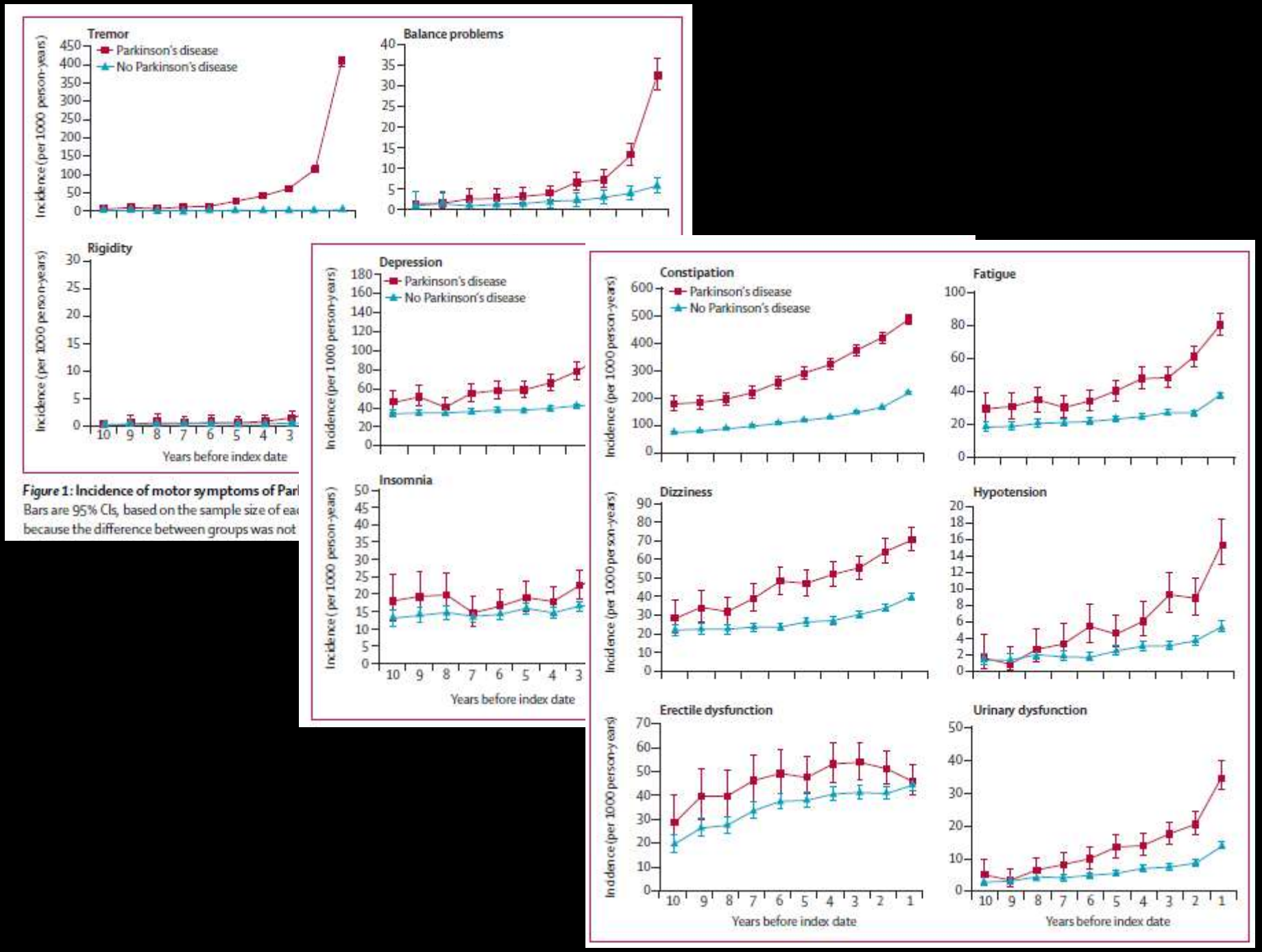


Figure 1: Incidence of motor symptoms of Parl
Bars are 95% CIs, based on the sample size of ea
because the difference between groups was not

Diagnostics summary

- Parkinsonism vs non-parkinsonism
- Parkinsonism
  - Idiopathic Parkinson's disease (80%)
    - Sporadic (90%)
    - Genetic (10%)
  - The rest
    - drug induced
    - associated with cerebrovascular disease
    - associated with hydrocephalus
    - post-traumatic
    - infectious diseases (post encephalitic)
    - toxic/metabolic
    - inherited metabolic (eg Wilson's, mitochondrial)
    - neurodegenerative disorders (PSP, MSA, CBS etc)
    - inherited degenerative disease (eg HD)
    - miscellaneous (eg tumours, subdural etc)

How to do it

- History
  - Inclusive/exclusive clues
- Examination
- (Tests)
- Follow up

History

- Prodromal stage (years)
  - Hyposmia
  - REM sleep behavioural disturbance
  - Constipation
  - Depression/anxiety
  - Dizziness
  - (fatigue, apathy, cognition, personality)

History

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- Exclusion criteria/red flags

History

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  - (fatigue, apathy, cognition, personality)
- Exclusion criteria/red flags
- Drugs!

Drugs

- Anti-psychotics (all except clozapine)
- Metoclopramide
- Valproate
- Tetrabenazine
- Reserpine
- Flunarizine/cinnarizine
- Lithium

Tremor

- Classic = unilateral rest tremor
  - One arm/leg
  - Jaw/chin
  - Not head
  - Worse when walking
  - Re-emergent tremor
- Less typically
  - Postural
  - Kinetic

Tremor differential

- Physiological
- ET
- Dystonic
- Drugs
- Functional
- FXTAS
- Toxins
- Orthostatic
- Neuropathy
- Cerebellar disease
- Etc.…

Any tests?

- Blood
  - Wilson's?
  - HIV?
  - Genetics?
- Imaging
  - Structural
  - Functional

Functional imaging in PD

- SPECT (gamma camera)
  - ^{123}I-FP-CIT
  - Dopamine active transporter (pre-synaptic)
- PET
  - ^{18}F-dopa
- (MIBG scintigraphy)

Genetic testing

- ~ 10% of PD
  - Your population
  - LRRK2 (AD)
  - Parkin (AR)
- Non-PD
  - FX premutation
  - Other PD mimics (NBIA etc)
  - Juvenile HD/phenocopies

Biomarkers

- Blood/serum and CSF markers
  - Alpha-synuclein
- Imaging markers
- Gait/movement analysis
- Etc…..

So, the secret…..?

- Follow patients long term
  - Listen and observe
  - Doubt yourself
  - Be prepared to get it wrong
  - Getting it wrong not the failure…
    - …….realising it is

Conclusions

- Parkinsonism/PD is clinical diagnosis
  - Bradykinesia absolute requirement
  - Prodromal stage
- Diagnostic criteria
- Tests rarely useful
- Follow up is key

Final words

- *….experts may be using a method of pattern recognition which goes beyond any formal diagnostic criteria.*
  Hughes A et al. Brain 2002;125:861-870

- *Clinical skills remain quintessential.*
  Schreglmann SR, Bhatia KP, Stamelou M. Intl R Neurobiol 2017;132:79-127