Atypical and secondary parkinsonism

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Parkinsonism

- **Synucleinopathy**
  - Parkinson’s Disease (PD)
  - Multiple System Atrophy (MSA)
  - Dementia with Lewy bodies (DLB)

- **Tauopathy**
  - Progressive Supranuclear Palsy (PSP)
  - Corticobasal degeneration (CBD)
  - Frontotemporal dementia (FTD)

Multiple system atrophy
MSA
MSA terminology

**OLD**
- Striatonigral degeneration (SND)
- Olivopontocerebellar atrophy (OPCA)
- Shy-Drager syndrome (SDS)

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

MSA epidemiology

- Estimated mean incidence 0.6 to 0.7 cases per 100,000 person-years (range 0.1-2.4 cases per 100,000 person-years)
- Estimated point prevalence 3.4 to 4.9 cases per 100,000 population, increasing to 7.8 per 100,000 among persons over 40 years
- Parkinsonian > cerebellar subtype in most countries (2:4:1)
  - Cerebellar subtype is more frequent in Japan → genetic or epigenetic factors?
- Disease onset in sixth decade, both sexes equally affected
- Mean survival from symptom onset is 6 to 10 years, few patients survive more than 15 years

Fancuilli and Wenning 2015
Table 1
Criteria for the diagnosis of probable MSA

- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and
- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar ocular motor dysfunction)

Table 2
Criteria for possible MSA

- A sporadic, progressive, adult (>30 y) onset disease characterized by
- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar ocular motor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features shown in table 3

Table 3
Additional features of possible MSA

- Babinisk sign with hyperreflexia
- Stridor
- Possible MSA-P
  - Rapidly progressive parkinsonism
  - Poor response to levodopa
  - Postural instability within 3 y of motor onset
  - Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar ocular motor dysfunction
  - Dysphagia within 5 y of motor onset
  - Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
  - Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
- Possible MSA-C
  - Parkinsonism (bradykinesia and rigidity)
  - Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
  - Hypometabolism on FDG-PET in putamen
  - Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET
MSA – “Red” flags

MSA and neuropsychiatric features

• Cognitive - executive dysfunction; dementia 31%
• Depression
  • ~40-85% have at least mild depression and 1/3\textsuperscript{rd} have moderate to severe depression
• Anxiety
  • Affects ~37%
• Apathy
  • Frequent, ~65%
• Excessive daytime sleepiness
  • More than 25%, unrelated to depression

Miki et al., 2020; Jellinger et al., 2020
Multidisciplinary presentation of MSA

MSA – Progressive course

Figure 3. Natural History of MSA. The premotor phase of MSA can last for months to years. Year 0 denotes the time of onset of motor symptoms. A diagnosis of definite MSA is not possible until the postmortem examination is performed.
Differential diagnosis

- Parkinson’s disease
- Other atypical parkinsonian syndromes
- Dementia with Lewy bodies
- Cerebellar ataxias
- Pure autonomic failure

Other investigations

- Sensitivity of clinical diagnosis of MSA ~ 88.2% (mov dis specialists), 64.3% general neurologists
- Brain imaging
  - MR Imaging – may be helpful, not always specific
  - PET/SPECT Imaging – MSA vs. cerebellar ataxias, not among parkinsonian syndromes
- Cardiac sympathetic imaging (MIBG) – preserved postganglionic presynaptic cardiac sympathetic nerve endings in MSA (vs. PD), though overlap present
- Autonomic testing (Valsalva, tilt table, sudomotor, thermoregulatory sweat test) – MSA vs. cerebellar ataxias, but not PD
- Anal sphincter EMG – degeneration of Onuf’s nucleus, MSA (vs. PD), though further studies nonconfirmatory (limited)
- Blood exosomes
  - Immunoprecipitated using neuronal and oligodendroglial markers (PD vs. MSA)?

Hughes et al., 2002; Jousta et al., 2014; Kim et al., 2015; Pellechia et al., 2020; Stankovic et al., 2021; Dutta et al., 2021
MSA - Imaging

- Cerebellar atrophy
- Brainstem atrophy
- Hot cross buns sign
- Hyperintense putaminal rim on T2/FLAIR

MSA - Pathology

- Neuronal loss and axonal degeneration, mainly in nigrostriatal and pontocerebellar systems
- Astroglial cytoplasmic inclusions and threads
- Myelin pallor and accompanying gliosis
- Hallmark = cytoplasmic ASYN positive glial cytoplasmic inclusions (GCIs) within oligodendroglial cells

Armstrong et al., 2007; Jellinger 2014; Kim et al., 2015
MSA - Treatment

• Motor
  • Parkinsonism - ~1/3 respond to levodopa; watch for OH and facial dyskinesias; gait/safety
  • Ataxia – consider amantadine; address gait/safety

• Non-motor
  • Bladder - oxybutynin, tolterodine, solifenacin, etc; botulinum toxin
  • Constipation – polyethylene glycol, bisacodyl, etc; lubiprostone, linaclotide (activates intestinal Cl channels and cGMP)
  • Sleep apnea – CPAP, BIPAP
  • RBD – clonazepam, melatonin
  • Stridor – CPAP, trach (Consensus statement, Cortelli et al., 2019)
  • Dysphagia (Consensus statement, Calandra-Buonaura et al., 2021)

MSA –Treatment (2)

• Orthostatic hypotension
  • Nonpharmacological – fluids, salt, gradual transitions, support hose, abdominal binder, avoid Valsalva, reduce or d/c anti-HTN
  • Pharmacological
    • Fludrocortisone (mineralocorticoid) - 0.1-0.5 mg/day
    • Midodrine (peripheral α1-agonist) - 5-10 mg TID
    • Pyridostigmine (cholinesterase inhibitor) - 30-60 TID
    • Droxidopa (L-DOPS, “prodrug” of NE), up to 600 mg TID
    • Atomoxetine (Shibao et al., 2021, single dose 18 mg)

• Supine hypertension – head up, NTG, clonidine
MSA research trials

• Polyphenol epigallocatechin gallate (2019)
  • Inhibits α-synuclein aggregation and reduces associated toxicity
  • DBPC trial, 52 weeks total with 48 weeks of treatment (n=67)
  • Primary endpoint - change in motor examination score of UMSARS
  • No difference in the mean change in UMSARS motor

• PD01A and PD03A (2020)
  • Active a-syn immunotherapies
  • Safety and tolerability
  • Early MSA (n=30)
  • SE – injection site reactions
  • Triggered antibody response targeting a-syn epitope

• Fluoxetine (2021)
  • DBPC, 12 weeks (n=81)
  • Primary endpoint – change in UMSARS total score
  • No difference in the mean change in UMSARS but + in MSA QoL emotional/social dimension

Levin et al., 2019; Meissner et al., 2020; Rascol et al., 2021

Dementia with Lewy Bodies

DLB
The terrorist inside my husband’s brain

I am writing to share a story with you, specifically for you. My hope is that it will help you understand your patient along with their spouse and caregivers a little more. And as for the research I am sure, perhaps this will add a few more facts behind the why you do what you do. I am sure there are already so many.

This is a personal story, soul-tinging and heart-breaking, but by sharing this information with you, I know that you can help make a difference in the lives of others.

As you may know, my husband Robin Williams had the little-known but deadly Lewy body disease (LBD). He died from suicide in 2014 at the end of an intense, frightening, and relatively swift progression at the hand of this disease’s symptoms and pathology. He was not alone in his cognitive experience with this neurologic disease. As you may know, almost 1.5 million North Americans are suffering similarly right now.

Although not alone, his case was extreme. Not until the summer’s report, 3 months after his death, would I know that it was difficult LBD that took him. All 4 of the doctors I met with afterward and who had reviewed his records indicated his case was one of the worst they had seen. He had about 40% loss of dopamine neurons and almost no neurons were free of Lewy bodies throughout the entire brain and brainstem.

Robin is and will always be a large-than-life spirit who was inside the body of a normal man with a human brain. He just happened to be that 1 in 6 who is affected by this disease.

Not only did I lose my husband to LBD, I lost my best friend, whom he left this world together, as if he was on the road. We would discuss our joys and triumphs, our fears and insecurities, and our concerns. Any obstacle he threw at us individually or as a couple were somehow surmountable because we had each other.

When LBD began sending a dozen symptoms our way, this foundation of friendship and love was our armor.

The color were changing and the air was crisp; it was already late October of 2012 and our second wedding anniversary. Robin had been under his doctors’ care. He had been struggling with symptoms that sound unrelated—constipation, urinary difficulty, hallucinations, insomnia, and a poor sense of smell—since 2010. He also had a slight tremor in his left hand that would come and go. For the time being, that was attributed to a previous shoulder injury.

On this particular weekend, he awoke having not slept. Having been by my husband’s side for many years already, I knew his normal reactions when it came to fear and anxiety. What would follow was markedly out of character for him. His fear and anxiety skyrocketed to a point that was alarming. I wondered profoundly: Is my husband a hypochondriac? Not until after Robin left us would I discover that a sudden and pronounced spike in fear and anxiety can be an early indication of LBD.

He was tested for Lewy theory and the results were negative. Like the rest of the symptoms that followed, they seemed to come and go at random times. Some symptoms were more persistent than others, but these

DLB terminology

Lewy body dementia

Parkinson’s disease dementia (PDD)

dementia with Lewy bodies (DLB)

www.lbda.org
DLB - Epidemiology

- 2\textsuperscript{nd} most frequent neurodegenerative dementia following AD
- In population-based and clinic-based studies, represents \(\sim 4\text{-}30\%\) of dementia cases
- Likely underrepresented in many clinical studies due to methodological issues
- In autopsy series, DLB represents greater \% than in clinical series, up to 31\% in some studies

Barker et al., 2002; Zaccai et al., 2005; Vann Jones et al., 2014

DLB criteria

Table 1: Revised\textsuperscript{1,2} criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

| Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur early. |
| Core clinical features (The first 3 typically occur early and may persist throughout the course.) |
| Fluctuating cognition with pronounced variations in attention and alertness. Recurrent visual hallucinations that are typically well formed and detailed. REM sleep behavior disorder, which may precede cognitive decline. One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity. |
| Supportive clinical features |
| Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypertrichosis; hypomimia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression. |

McKeith et al., 2017
Multiple clinical features
Biomarkers in DLB criteria: AD vs. DLB vs. NC

Figure 1. Coronal T1-weighted MRI and 18F-FDG PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC).

Figure 2. 18F-FDG PET/MR imaging in patients with Alzheimer disease (AD) dementia with Lewy bodies (DLB), and age-matched normal controls (NC).

Images taken 2 hours after injection are shown in 2 color scales, and optical regions of interest are shown on the head (dotted circle) and upper mediastinum (rectangle). Heart-to-mediastinum (H/M) ratios are standardized to the values comparable to the medium-energy general-purpose collimator condition. Reproduced with permission from Dr. Keioh Nakaizumi, Department of Nuclear Medicine, Kanazawa University.

DLB - Pathology

McKeith et al., 2005; McKeith 2007; Jellinger 2018
Amyloid and tau biomarkers differently associated with DLB clinical features

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Isolated contributions of β-amyloid and tau biomarkers</th>
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<tr>
<td>Age, y</td>
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<td>Education, y</td>
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<td>MMSE total score</td>
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<td>Fluctuations, %</td>
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<td>Parkinsonism, %</td>
<td>83</td>
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<tr>
<td>Probable RBD, %</td>
<td>66</td>
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</table>

Abbreviations: A = β-amyloid; MMSE = Mini-Mental State Examination; RBD = REM sleep behavior disorder; T = tau; + = abnormal values; − = normal values. Mean (SD) is used for continuous variables and count (%) for categorical variables.
* The values of p < 0.05 from independent univariate models reported in each row. Values are age and sex adjusted when appropriate with a random blocking variable for center.

Ferreira et al., 2020

RT-QuIC

- Real-time quaking-induced conversion (RT-QuIC) assay
- Detect these αSyn aggregates in the brain tissue and CSF
- Differentiate synucleinopathies from non-synucleinopathies
- Identified MCI-LB vs. MCI-AD and unspecified MCI
  - Accuracy 97.3%, 93.7%

Bongianni et al., 2019; Bargar et al., 2021; Rossi et al., 2021
A few assessment clinical pearls

• Clinical neuropsychological profile similar between DLB and PDD
• More differences between LBDs vs. AD

• Noise pareidolia test
  • Evokes visual illusions, surrogate marker for visual hallucinations in DLB
  • Discriminates DLB vs. AD
  • Brief test, good test-retest/inter-rater reliability, moderately correlated with NPI-halluc

DLB - Treatment - Motor

• Levodopa in DLB
  • Acute challenge (n=14), improved UPDRS III score with 36% classified as responders
  • Acute challenge (n=11) and 3 month treatment, no adverse cognitive or neuropsychiatric effects after 3 months (doses ~100 mg/d)
  • Effect on psychosis (n=19) – only 1/3rd had motor benefit and of these, 1/3rd had worsened psychosis. Only 4/19 (22%) had motor benefit w/o exacerbation of psychosis

• Zonisamide in DLB
  • Phase 2 (n=137) and Phase 3 (n=319) DBPC, adjunct to levodopa
  • Primary endpoint: UPDRS part 3 at week 12
  • Improvement in UPDRS 3 in ZNS 25 mg and 50 mg vs. placebo
  • No change in NPI-10/BPSD

Molloy et al., 2005, 2006; Goldman et al., 2008; Murata et al., 2018, 2020
**DLB - Treatment - Nonmotor**

- Orthostatic hypotension – similar to PD and MSA
- Bladder – similar but caution re: CNS/neuropsychiatric effects
- Constipation – similar - polyethylene glycol, bisacodyl, etc
- RBD – clonazepam, melatonin
  - Nelotanserin – no difference Phase 2 study
- Daytime sleepiness – wakefulness promoting agents (modafinil, armodafinil)
  - Armodafinil – DLB, 12 week pilot, 125-250 mg/d, 17 completed
    • Improvement on ESS, MWT, CGIC, NPI, Caregiver QoL
- Depression, anxiety – SSRIs, SNRIs, buproprion, anxiolytics
- Apathy – very difficult!
- Fluctuating cognition – very difficult!

**DLB – Treatment - Dementia**

- Dementia
  - Cholinesterase inhibitors (rivastigmine and donepezil) have Class I evidence for efficacy in DLB
  - DLB often greater treatment response than AD, due to profound cholinergic deficits
    • Donepezil approved in Japan
  - Memantine – mixed results
  - Intepirdine - negative

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Boot et al., 2013; Lapid et al., 2017; Armstrong 2019; Stefani et al., 2021

Rolinski et al., Cochrane 2012; Goldman and Weintraub 2015; Pagan et al., 2016; Lang et al., 2021
DLB – Treatment -Psychosis

• Nonpharmacological
  • Similar to PD with home modifications and coping strategies
  • Exclude underlying medical illness
  • Discontinue exacerbating meds (e.g., pain, bladder, CNS-meds)
  • Reduce or discontinue any parkinson meds

• Pharmacological
  • Antipsychotics
    • Quetiapine, starting at 12.5 mg/d; monitor for sedation and OH
    • Clozapine, starting at 6.25 mg/d (lab monitoring)
    • Black box warnings
    • Pimavanserin? (Positive results from HARMONY dementia-related psychosis trial but FDA rejected approval 4/21)
  • Cholinesterase inhibitors
  • Nelotanserin - no change SAPS-PD

Research criteria for the diagnosis of prodromal dementia with Lewy bodies

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Abstract

The prodromal phase of dementia with Lewy bodies (DLB) includes (1) mild cognitive impairment (MCI), (2) delirium-onset, and (3) psychiatric-onset presentations. The purpose of our review is to determine whether there is sufficient information yet available to justify development of diagnostic criteria for each of these. Our goal is to achieve evidence-based recommendations for the recognition of DLB at a predementia, symptomatic stage. We propose operationalized diagnostic criteria for probable and possible mild cognitive impairment with Lewy bodies, which are intended for use in research settings pending validation for use in clinical practice. They are compatible with current criteria for other prodromal neurodegenerative disorders including Alzheimer and Parkinson disease. Although there is still insufficient evidence to propose formal criteria for delirium-onset and psychiatric-onset presentations of DLB, we feel that it is important to characterize them, raising the index of diagnostic suspicion and prioritizing them for further investigation.
Progressive Supranuclear Palsy

PSP

PSP - Epidemiology

- Reported to comprise about 5% of parkinsonian patients in a movement disorder clinic
- Crude prevalence of 1.39-14.3 per 100,000
- Incidence of 0.3-1.1 cases per 100,000 per year
- Misleading and likely underrepresented in many clinical studies due to methodological issues, definitions, lack of autopsy confirmation
- Series mixed regarding M:F

Burn et al., 2000; Williams et al., 2009
PSP – Clinical features

- Progressive disorder
- Age onset ≥ 40
- Parkinsonism, minimal levodopa response
- Often symmetric at onset
- Falls in the first year
- Vertical supranuclear gaze palsy
- Saccade abnormalities ("round the house," "zig-zag")
- Dysarthria
- Axial rigidity
- Blepharospasm or apraxia of eyelid opening
- Cognitive and behavioral problems
- Frontal lobe dysfunction

Abate et al., 2020; Marsili et al., 2020; Rowe et al., 2021

MDS PSP criteria

- Inclusion criteria
  - Sporadic occurrence
  - Age 40 or older
  - Gradual progression
- Exclusion criteria...
- Supportive features
  - Clinical: levodopa-resistance; hypokinetic, spastic dysarthria; dysphagia; photophobia
  - Imaging: Predominant midbrain atrophy or hypo metabolism; post-synaptic stratal DA degeneration
PSP - Imaging

Richardson’s (PSP-RS/ NINDS-SPSP)

PSP-Parkinson’s (PSP-P)

Pure akinesia with gait freezing (PAGF)

Corticobasal syndrome (CBS)

Progressive nonfluent aphasia (nfvPPA)

Frontotemporal dementia (bvFTD)

PSP neuropathology

Multiple phenotypes

Modified from Adam Boxer and Irene Litvan

Williams and Lees 2009; Lopez et al., 2016; McFarland 2017
MAPT locus
Most strongly linked with PSP risk
OR for MAPT H1/H1 carriers is 5.5
Higher than the OR for APOE e3/e4 genotype for AD
GWAS studies – new genetic risk factors (STX6, EIF2AK3, MOBP)
Management

- **Motor**: Dopaminergic agents, PT, OT
- **Dystonia**: Botulinum toxin injections
- **Speech/swallowing**: SLP
- **Orthostatic hypotension**: Salt, fludrocortisone, midodrine, droxidopa
- **Neurogenic bladder**: solifenacin, mirabegron
- **Mood**: Antidepressants
- **Apathy**: cholinesterase inhibitors, stimulants
- **Cognition**: cholinesterase inhibitors, memantine
- **Gastroparesis**
Trials and pipeline

- Agents tried...negative
- Riluzole, Lithium, Tideglusib (phase 2, GSK-3 inhibitor), Davunetide (phase 2-3, microtubule stabilizer), Anti-tau antibody (ABBV-8E12)

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Table 2: Planned or ongoing clinical trials involving tau therapeutics

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**Safety and efficacy of tivalonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial**

**Summary**

**Background** Progressive supranuclear palsy is a neurodegenerative disorder associated with tau protein aggregation. Tivalonemab (ABBV-8E12) is a monoclonal antibody that binds to the N-terminus of human tau. We assessed the safety and efficacy of tivalonemab for the treatment of progressive supranuclear palsy.

**Methods** We did a phase 2, multicentre, randomised, placebo-controlled, double-blind study at 66 hospitals and clinics in Australia, Canada, France, Germany, Italy, Japan, Spain, and the USA. Participants aged 40-90 years diagnosed with possible or probable progressive supranuclear palsy who were symptomatic for less than 5 years, had a reliable study partner, and were able to walk five steps with minimal assistance were randomly assigned (1:1:1) by interactive response technology to tivalonemab 2000 mg, tivalonemab 4000 mg, or matching placebo administered intravenously on days 1, 3, and 29, every 28 days through the end of the 52-week treatment period. Randomisation was done by the randomisation specialist of the study sponsor, who did not otherwise involve investigators. The primary endpoint was the change from baseline to week 52 for the Progressive Supranuclear Palsy Rating Scale (PSRFRS) total score in the intention-to-treat population. Adverse events were monitored in participants who received at least one dose of study drug. Prespecified interim futility criteria were based on a model-based effect size of 0 or lower when 60 participants had completed the 32-week treatment period and 0.12 or lower when 120 participants had completed the 52-week treatment period. This study is registered at ClinicalTrials.gov, number NCT01985719.

**Findings** Between Dec 12, 2016, and Dec 31, 2018, 464 participants were screened. 378 were randomised. The study was terminated on July 3, 2019, after prespecified futility criteria were met at the second interim analysis. A total of 377 participants received at least one dose of study drug and were included in the efficacy and safety analyses (2000 mg, n=124; 4000 mg, n=123; placebo, n=130). Least squares mean change from baseline to week 52 for PSFRS-R was similar in all groups (between-group difference -1: placebo: 2000 mg, 0.0-0.3% CI -1.2 to 2.4, effect size 0.000, p=0.99; 4000 mg, 0.1 to 3.6; -0.105, p=0.46). Most participants reported at least one adverse event (2000 mg, 111 [55%]; 4000 mg, 111 [50%]; placebo, 108 [86%]). Full was the most common adverse event (2000 mg, 43 [33%]; 4000 mg, 43 [33%]; placebo, 33 [26%]). Full was the most common treatment-emergent serious adverse event (2000 mg, five [4%]; 4000 mg, six [5%]; placebo, six [5%]). 26 deaths occurred during the study (2000 mg, nine [7%]; 4000 mg, nine [7%]; placebo, eight [6%]) but none was drug related.

**Interpretation** A similar safety profile was seen in all treatment groups. No beneficial treatment effects were recorded. Although this study did not provide evidence of efficacy in progressive supranuclear palsy, the findings provide potentially useful information for future investigations of passive immunisation using tau antibodies for progressive supranuclear palsy.
Corticobasal degeneration (CBD)

CBD - Early history/epidemiology

- First described “corticodentatonigral degeneration with neuronal achromasia”
- 3 patients with asymmetric, akinetic-rigid syndrome with cerebral cortical dysfunction
- Widespread deposition of 4-R tau in neurons and glia
- Pathology predicted antemortem in only 25-56% of cases
- Corticobasal syndrome – only one type of CBD
- Prevalence of 4.9-7.3 per 100,000, incidence 0.62-0.92 per 100,000 per year

Rebeiz et al., 1967; Gibb et al., 1989
CBD – Clinical features

- Gradual onset
- Age ≈ 60 years
- Marked asymmetry
- Parkinsonism
- Apraxia
- Alien limb
- Cortical sensory loss
- Dystonia
- Myoclonus
- Dementia
- Aphasia

CBD

- Imaging
  - Asymmetric fronto-parietal atrophy
  - Often seen on MRI or SPECT

- Pathology
  - Asymmetric fronto-parietal atrophy
  - Balloonened, achromatic neurons
  - Astrocytic plaques
  - Tau
CBD phenotypes and criteria

Table 4 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration²⁻⁷

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable corticobasal syndrome</td>
<td>Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) oral bruxism or limb apraxia, e) cortical sensory deficit, f) alien limb phenomenon (more than simple levitation)</td>
</tr>
<tr>
<td>Possible corticobasal syndrome</td>
<td>May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) oral bruxism or limb apraxia, e) cortical sensory deficit, f) alien limb phenomenon (more than simple levitation)</td>
</tr>
<tr>
<td>Frontal behavioral–spatial syndrome</td>
<td>Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial defects</td>
</tr>
<tr>
<td>Nonfluent/agrammatic variant of primary progressive aphasia</td>
<td>Effortful, agrammatic speech plus at least one of: a) impaired grammatical sentence comprehension with relatively preserved single word comprehension, or b) grasping, distorted speech production (apraxia of speech)</td>
</tr>
<tr>
<td>Progressive supranuclear palsy syndrome</td>
<td>Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades</td>
</tr>
</tbody>
</table>

Zijlmans JC et al., Mov Dis 2004; Vizcarra et al., 2015; Rektor et al., 2018

Table 5 Diagnostic criteria for corticobasal degeneration

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Clinical research criteria for probable sporadic CBD</th>
<th>Clinical research criteria for possible CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum duration</td>
<td>Insidious onset and gradual progression</td>
<td>Insidious onset and gradual progression</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Family history</td>
<td>Exclusion</td>
<td>Permitted</td>
</tr>
<tr>
<td>Permitted phenotypes</td>
<td>1) Probable CBD or 2) FRS or NAV plus at least one CBS feature b-f</td>
<td></td>
</tr>
<tr>
<td>Genetic mutation</td>
<td>Exclusion</td>
<td>Permitted</td>
</tr>
</tbody>
</table>

Vascular parkinsonism

- Lower body parkinsonism
- Early gait impairment
- Corticospinal tract signs (hyperreflexia, extensor plantar response)
- Urinary incontinence
- Pseudobulbar signs
- “Lacunar” infarcts or white matter hyperintensities
Drug induced parkinsonism

- May be similar to PD
  - Rest tremor, asymmetry, gait
- 8-12% of parkinsonism
- 2.5-3.3/100,000 person/year
  - Increases with advanced age
  - F > M
  - Unmasked PD? Dual-hit hypothesis
- Blockade of D2 receptors
- Treatment
  - Stop causative agent
  - DA or anticholinergic medications

Other parkinsonisms

- Wilson’s disease
- Juvenile Huntington’s disease
- Spinocerebellar ataxia types 2 and 3
- Neuronal brain iron accumulation
- Dystonia-parkinsonism syndromes
- Alzheimer’s disease plus parkinsonism
- Toxins – MPTP, CO, manganese, dopaminergic blockers
- Metabolic – hypoxia, hepatocerebral degeneration
- Whipple’s disease
Thank you for your attention!

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