PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL DEGENERATION

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Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD) are two closely related sporadic late-life onset neurodegenerative diseases associated with a variety of motor and behavioral clinical phenotypes due to the deposition and aggregation of 4 repeat tau. This lecture (summarized in the table below and accompanying selected readings) will provide an update on our current understanding of these disorders.

	Progressive Supranuclear Palsy	**Corticobasal Degeneration**
Demographics	Mean age of onset for both ~ 65 yr (no cases <40); Disease duration slightly longer in PSP (~8 yr vs 6.6); no gender predilection. Prevalence of PSP est. 6/100,000 – likely an underestimate given increasing recognition of variant PSP (vPSP) cases. Prevalence of CBD unknown (<< PSP).	
Etiology	Unknown; sporadic; Cluster of PSP in France suggests environmental factors. Genetic predisposition: • *MAPT*: mutations (largely involving exon 10) can cause identical pathologies and clinical phenotypes, homozygosity at H1 haplotype and H1c sub-haplotype, rare coding and non-coding variants • Other genetic risk factors: GWAS show other genes in common – e.g., *MOBP* – SNP more strongly correlates with gene coding for Appoptosin (involved in caspase cleavage of tau)	
Pathology - Regional distribution of pathology accounts for varying clinical phenotypes (see below)	4R tauopathy: Neuronal loss, gliosis, NFTs, neuropil threads, **tufted astrocytes** and oligodendroglial coiled bodies in basal ganglia and brainstem (and elsewhere) Mixed pathology not uncommon on postmortem: concomitant AD, PD, cerebral white matter rarefaction, vascular disease including cerebral amyloid angiography.	4R tauopathy: Cortical and striatal tau-positive neuronal & glial lesions, neuronal loss in cortex and substantia nigra, tau +ve thread-like lesions in both WM & GM, **astrocytic plaques**, argyophilic grains, ballooned neurons (supportive)
Clinical Phenotypes	Richardson syndrome (PSP-RS): Highest specificity for PSP pathology, only ~25% present in this fashion; Parkinsonism (PSP-P); Pure akinesia with gait freezing (PSP-PAGF); Corticobasal syndrome (PSP-CBS); Non-fluent variant primary progressive aphasia (PSP-nfvPPA) + apraxia of speech (AOS); Behavioral variant frontotemporal	Very low diagnostic accuracy in life. Corticobasal syndrome (CBD-CBS) – best recognized but < 30% present in this fashion and < 40% at final Dx (several other causes – see below); Frontal behavioral-spatial syndrome (CBD-bvFTD); Nonfluent/agrammatic variant of primary progressive aphasia (CBD-nfvPPA) + apraxia of speech (AOS); Progressive supranuclear palsy

	dementia (PSP-bvFTD); Predominant cerebellar ataxia (PSP-C); Others: limited phenotypes (e.g., postural instability, oculomotor), unusual phenotypes (e.g., primary lateral sclerosis)	syndrome (CBD-PSPS) (essentially a Richardson variant); Others – AD-like dementia, parkinsonism, posterior cortical atrophy, progressive spasticity, mixed.
Clinical Diagnostic Accuracy	At presentation many cases show either overlapping features of several phenotypes, or features not fitting proposed classification criteria for PSP phenotypes → new diagnostic criteria under development. Need for reliable diagnosis early in disease course for entry into trials of disease modifying therapies.	Recently proposed diagnostic criteria remain problematic with up to 1/3 of pathologically proven cases not diagnosed in life. Should improve considerably using biomarkers to exclude AD. Diagnostic inaccuracy a major problem for enrollment in trials of disease modifying therapies → combine with PSP as 4R tauopathies.
Differential Diagnosis (very broad for both if considering all possible phenotypes)	PSP-RS look-alikes: CBD, CJD, MSA, motor neuron disease, spinocerebellar ataxias, AD, DLB, argyrophilic grain disease, Whipple disease, Niemann-Pick C, Gaucher's disease, mitochondrial disorders, vascular disorders (incl stroke, cerebral amyloid angiopathy, CADASIL), progressive encephalomyelitis with rigidity and myoclonus (PERM); Genetic disorders: FTLD (see Familial CBS), Niemann Pick type C (NPC1, NPC2), Kufor Rakeb syndrome (ATP13A2), Perry syndrome (DCTN1), mitochondrial diseases (POLG, mitochondrial mutations), dentatorubral pallidoluysian atrophy (ATN1), prion-related diseases (PRNP), Huntington's disease (HTT), spinocerebellar ataxia (ATXN1, 2, 3, 7, 17)	Corticobasal Syndrome: • PSP • AD (episodic memory, visuoperception, CSF, PET) • Pick's • Vascular • CJD (rapid progression; often death in < 1yr) • TDP-43opathy • Argyrophilic grain disease • Others ("CBS" often loosely applied) Familial CBS: • FTLD*: MAPT*, *PRGN*, *C9orf72*, *FUS*, *TARDBP, VCP, CHMP2B)* • Others (e.g., *PSEN1*)
Biomarkers / Diagnosis (other than tau-PET) Still no adequately powered studies in autopsy confirmed cases.	Anatomic imaging: PSP-RS – atrophy of midbrain and superior cerebellar peduncles (SCP) and MR parkinsonism index (MRPI) – distinguishes PSP from other parkinsonian disorders but probably insensitive to early disease. Metabolic imaging: FDG-PET– hypometabolism in frontal cortex,	Anatomic and metabolic imaging – only correlate with the clinical CBS not with the underlying pathology. Major problems with all studies: diagnostic inaccuracy and lack of autopsy confirmation. Importance of excluding AD in

Biomarkers urgently needed for mildly symptomatic/pre-symptomatic cases	caudate, midbrain, and thalamus; diagnostic utility not established, probably correlates more with clinical phenotypes. Blood / CSF: nothing confirmed; CSF tau normal or low (vs elevated in AD); elevated neurofilament light chain (NfL) (CSF & blood) – change over time may be a useful index of disease progression. Physiology – changes in saccade velocity and gain (including changes over time).	making Dx – use of established biomarkers of AD (CSF T-tau, P-tau and Aβ42, amyloid PET)
Tau-specific PET imaging ligands:	Several Tau-PET ligands under study ^{18}F-AV-1451 (T-807) – autoradiography studies indicate strong binding to PHFs in AD but little binging to straight filaments in 4R tauopathies; however, single case reports show promising evidence for binding in vivo (CBD). ^{18}F-THK5351 – promising results in CBS (likely CBD)	
Pathogenesis	Multiple cellular mechanisms proposed. Cell-to-cell spread of tau in specific brain networks connected functionally and neuroanatomically may account for phenotypes. Injection of brain tissue from human disease into transgenic (and less so non-transgenic) mice recapitulates neuropathological features of the individual diseases - ? evidence for different strains of transmissible tau (similar to prion diseases) Tau transgenic animal models – may be useful in testing therapeutics Both Tau gain-of-function and Tau loss-of-function mechanisms proposed	
Therapeutics-Symptomatic	Nothing reliably effective; L-dopa for parkinsonism, amantadine; BTX for eyelid abnormalities (blepharospasm, "apraxia of lid opening"	Most ineffective; rarely is L-dopa useful; clonazepam for myoclonus; BTX for dystonia
Therapeutics-Disease Modifying	Negative RTCs of riluzole, tideglusib, davunetide, coQ10, valproic acid in PSP Tau loss of function therapies: • Microtubule stabilizing agents Tau gain of function therapies: • Immunotherapeutic approaches – active and passive immunization • Small molecules targeting aggregation or post-translational modification • Antisense oligonucleotides and splicing modulators • Microglial targeted approaches • Enhanced autophagy and other strategies	

Selected Reading

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