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From Neuropathology to Symptom and Network: Lessons from FTLD in Primary Progressive Aphasia (PPA)

Primary Progressive Aphasia (PPA) can be caused either by Frontotemporal Lobar Degeneration (FTLD) or Alzheimer's disease neuropathologic changes (ADNC). In 118 consecutive PPA brain autopsies, the primary neuropathology was ADNC in 42%, and FTLD in 58%. Within the 58% of PPA autopsies with FTLD, Corticobasal Degeneration (CBD) or Progressive Supranuclear Palsy (PSP) neuropathology accounted for 24%, Pick's disease accounted for 10%, transactive response DNA binding proteinopathy type A (TDP(A)) accounted for 10%, TDP(C) accounted for 11%, and infrequent entities accounted for 3%. Survival was longest in TDP(C) (13.2±2.6 years) and shortest in TDP(A) (7.1±2.4 years). Each neuropathologic entity had preferred but not invariant clinical correlates. Seventy-seven percent of those with logopenic aphasia had ADNC, 56% of agrammatics had CBD/PSP or Pick's, and 89% of semantics had TDP(C). Word comprehension impairments had strong predictive power for determining underlying neuropathology, positive for TDP(C) and negative for ADNC. Cortical atrophy at initial stages was least extensive in CBD/PSP and most extensive in TDP(A). Atrophy encompassed posterior frontal but not temporoparietal cortex in CBD/PSP, anterior temporal but not frontoparietal cortex in TDP(C), temporofrontal but not parietal cortex in Pick's, and all 3 lobes in TDP(A). The one common denominator was asymmetric atrophy overwhelmingly favoring the language-dominant left hemisphere throughout the course of disease. Some entities such as Pick's disease were heterogeneous in clinical manifestation but not anatomic distribution while others such as TDP(C) were homogeneous both anatomically and clinically. These clinicopathologic patterns show that the nature of the language impairment (aphasia) in each case reflects complex interactions among cellular affinities of the degenerative disease, constitutive biology of brain asymmetry, developmental vulnerabilities of the language network, and functional anatomy of the affected person. Although not a common disease, PPA offers unique opportunities for exploring principles of selective vulnerability and the neuroanatomy of language.