Tauopathies

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Case-Based Questions (please see page 3 for answers)

1.	A 95-year-old man with a 10-year history of slowly progressive short term memory loss dies of congestive heart failure. Autopsy examination of the brain reveals Thal amyloid stage 0, neurofibrillary tangles in the entorhinal cortex and hippocampal pyramidal layer, and no neocortical neuritic plaques. The best neuropathologic diagnosis is:	
	a.	Alzheimer disease neuropathologic change, low stage
	b.	Incidental progressive supranuclear palsy
	c.	Normal for age
	d.	Primary age-related tauopathy

2.	Which of the following procedures would be most definitive in distinguishing progressive supranuclear palsy from Pick disease?	
	a.	Immunohistochemistry of frontal neocortex for phospho-tau
	b.	Immunohistochemistry of subcortical white matter for phospho-tau
	c.	Immunohistochemistry of temporal neocortex for 3R and 4R tau
	d.	Immunohistochemistry of temporal neocortex for beta-amyloid

3.	A 52-year-old woman presents with a 2-year history of insidious memory loss. Family history is remarkable for dementia in her grandfather; there is no family history of Parkinsonism. Physical examination reveals asymmetric motor apraxia. Over the next 4 years, memory function worsens, and she develops axial rigidity and mild alien limb phenomenon, and she dies at age 56. At autopsy, there are abundant neocortical tangles and plaques that are immunoreactive for both 3R and 4R tau. Beta-amyloid immunohistochemistry shows Thal stage 5. The best neuropathologic diagnosis is	
	a.	Alzheimer disease neuropathologic change, high stage
	b.	Corticobasal degeneration
	c.	FTDP-17
	d.	Progressive supranuclear palsy

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Question 1 Correct Answer and Rationale: **D**

Primary age-related tauopathy (PART). PART is defined by the presence of neurofibrillary tangles in the absence of amyloid pathology, and rarely exceeds Braak NFT stage IV. Clinically, PART is more common in the "oldest old" subjects and cognitive impairment is usually slowly progressive and often limited in severity. The presence of tau pathology, even in very old subjects, while common, is not "normal." The absence of amyloid excludes ADNC. PSP cannot be diagnosed on the basis of NFT restricted to medial temporal lobe structures.

Question 2 Correct Answer and Rationale: **C**

IHC of temporal neocortex for 3R and 4R tau. Both PSP and Pick disease can involve neocortex, but their 3R and 4R tau IHC staining patterns are mutually exclusive – Pick lesions show 3R tau immunoreactivity, while PSP lesions show 4R tau staining. Phospho-tau IHC of neocortex may be useful for distinguishing Pick bodies from PSP lesions structurally, but this would not be as definitive as demonstrating restricted 3R or 4R tau pathology. Subcortical while matter may show abnormalities in many of the tauopathies, but again, would not be as definitive as demonstrating restricted 3R or 4R tau immunostaining. Beta amyloid IHC is of no benefit in differentiating these 2 entities.

Question 3 Correct Answer and Rationale: **A**

Alzheimer disease neuropathologic change, high stage. While some of the clinical features suggest corticobasal syndrome (CBS), the presence of both 3R and 4R immunoreactivity in the neocortical plaques is characteristic of AD-type neuritic plaques, and Thal stage 5 is also consistent with advanced ADNC. CBS is not specific for underlying CBD neuropathology, and ADNC can be seen as the underlying pathology in CBS. Glial plaques of CBD consist of 4R tau only, as do the lesions of PSP. The diagnosis of "FTDP-17" has fallen into disfavor because the neuropathology is variable, but in any case, mutations in the tau gene on chromosome 17 virtually never result in ADNC.