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Update on the Neuropathological Diagnosis of Frontotemporal Dementias

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Previous criteria for Frontotemporal Dementia have primarily been designed for research purposes (1–5). An international group of experts on clinical and neuropathological aspects of frontotemporal dementia (FTD) recently re-assessed criteria for the diagnosis of FTD at a meeting entitled ''The Frontotemporal Dementia and Pick's Disease Criteria Conference'' held at the National Institutes of Health in Bethesda, MD on July 7, 2000 (see ref #1 and the roster of meeting participants in the Acknowledgments). Building upon a substantial literature on these disorders, the goal of the conference was to update previous FTD diagnostic criteria, taking into account recent research advances to refine guidelines for the clinical and neuropathological diagnosis of FTD (1). Here we provide a brief overview of the most salient points of the neuropathology recommendations for disorders included among FTDs.

Although Pick's disease can be considered the prototype of FTDs, in the last 3 decades it became increasingly clear to several research groups that there were a number of other distinct FTD variants that lacked the lobar atrophy and related neuropathology of Pick's disease (1). This prompted the use of a number of different names to designate these disorders, including FTD, frontal lobe degeneration of the non-Alzheimer-type, frontotemporal lobar degeneration (FTLD), dementia lacking distinct histopathology (DLDH), progressive aphasia and semantic dementia (1). Moreover, since several kindreds with FTD and parkinsonism linked to chromosome 17 were shown to have pathogenic *tau* gene mutations, the term FTDP-17 was used to refer to this hereditary group of FTDs, while a less well-characterized disorder in other patients with evidence of FTD as well as clinical and pathological findings of motor neuron disease (MND) has been designated FTD with MND, and hereditary forms of this disease have been linked to chromosome 9 (1). Since these and other terms have been used to refer to FTDs, thereby leading to a nearly impenetrable nomenclature, conference participants recommended that FTD be used as the clinical diagnostic term for these disorders, while FTLD and the other terms listed in this paper were recommended for the currently known neuropathological variants of FTDs (1).

While gross examination of postmortem brain from FTD patients often show frontotemporal atrophy, microscopic and other studies are needed to distinguish FTD variants from Alzheimer disease (AD), dementia with Lewy bodies (DLB), and other disorders (Fig. 1). The brain regions to be examined as well as the most relevant diagnostic methods are described in the conference report and previous citations therein (1). Notably, it was recommended that traditional histochemical methods be complemented by more sensitive immunohistochemical techniques to detect tau pathology, as well as by immunohistochemistry for ubiquitin since some lesions in FTDs are negative for tau yet positive for ubiquitin (1). Similarly, other diagnostically relevant pathologies (e.g. ballooned or achromatic neurons) are most effectively detected by immunostaining with antibodies to neurofilament or alpha-B-crystallin proteins, and the same applies to Lewy bodies (LBs) and related lesions in neurodegenerative synucleinopathies that require the use of antibodies to alpha-synuclein (1), though other techniques also may assist in establishing a diagnosis of FTD subtypes. For example, Western blot analyses of tau proteins separate disorders into those with and without insoluble tau, and the profile of insoluble tau differentiates those with a predominance of 3 microtubule-binding repeats (3R tau), 4 microtubule-binding repeats (4R tau), or both 3R and 4R tau (2, 3), while recent studies suggest that FTLD shows reduced soluble tau, no insoluble tau, and normal tau mRNA levels (4).

Towards an Updated Neuropathological Classification of FTDs

Consistent with the views embodied in consensus criteria for the postmortem diagnosis of AD that only probabilistic statements can be made about relationships between neuropathology and clinical manifestations (5), the FTD conference participants acknowledged that the clinical features of FTD do not predict the underlying disease and that neuropathology alone cannot establish whether or not a patient had FTD (1). Further, the conference

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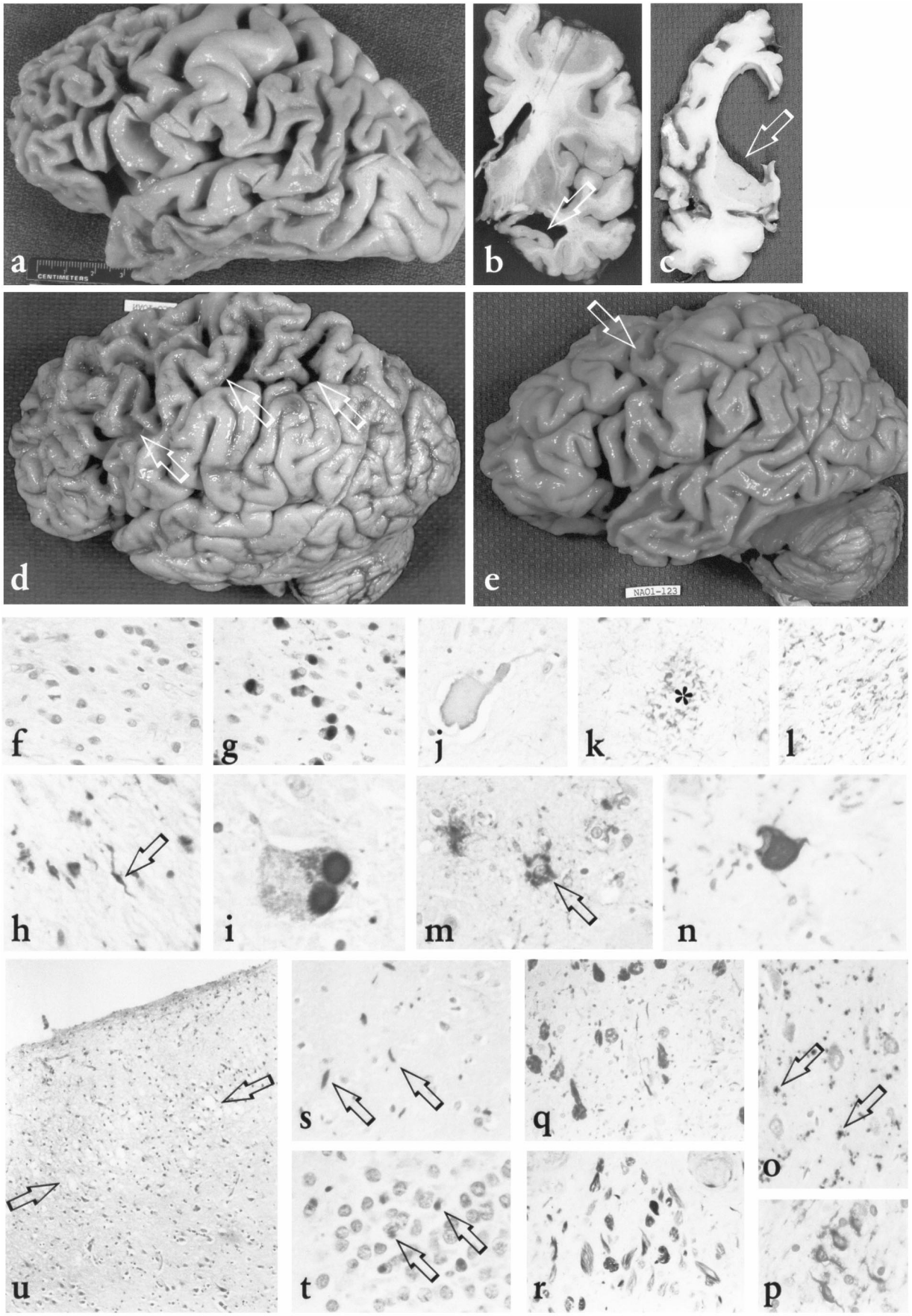

report emphasized the need to exclude other brain disorders that could account for the clinical syndrome to establish a neuropathological diagnosis of an FTD subtype, and that there should be a plausible correlation between the neuropathology and the clinical findings in patients with FTD (1). Informed by these principles, the meeting participants recommended the following neuropathological classification of FTDs: 1) When the neuropathology primarily includes tau positive lesions, neuron loss, gliosis and predominantly insoluble 3R tau, the likely diagnoses are a) Pick's disease and b) FTD with parkinsonism linked to chromosome 17 (FTDP-17). 2) When the neuropathology primarily includes tau positive lesions, neuron loss, gliosis, and predominantly insoluble 4R tau, the likely diagnoses are a) corticobasal degeneration, b) progressive supranuclear palsy, and c) FTDP-17. 3) When the neuropathology primarily includes tau positive inclusions, neuron loss, gliosis, and insoluble 3R and 4R tau, the likely diagnoses are a) neurofibrillary tangle dementia and b) FTDP-17. 4) When neuropathology primarily includes frontotemporal neuronal loss and gliosis, no tau/ubiquitin positive inclusions, no insoluble tau, and reduced soluble tau, the likely diagnosis is FTLD (also known as DLDH). 5) When neuropathology primarily includes frontotemporal neuronal loss and gliosis with ubiquitin-positive, tau-negative inclusions and without detectable amounts of insoluble tau with or without MND, but MND-type inclusions are present, the likely diagnoses are a) FTLD with MND and b) FTLD with MND-type inclusions, but without MND.

While the recommended neuropathological classification of FTDs that emerged from this conference was based on recent advances in understanding the structural neuropathology of these disorders, conference participants also drew upon similar advances in biochemical, molecular biological and genetic studies, and they acknowledged the possible existence of other yet to be defined FTD subgroups (designated as ''other'') in each of the 5 diagnostic categories summarized above. In addition, a comprehensive and practice-oriented algorithm for the diagnosis of FTDs was included in the conference report (1). Finally, the conference participants emphasized that their recommendations were the result of an iterative process that drew upon previous efforts to improve the diagnosis of FTDs, but that efforts to validate and refine these criteria should continue in order to improve methods for the early and accurate diagnosis of FTDs and hasten discovery of effective strategies to treat them.

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Fig. 1. Composite figure showing representative macroscopic (a–e) and microscopic (f–p) findings in various FTD subtypes. a: Pick's disease brain showing frontal and temporal lobar atrophy, with less obvious atrophy of inferior parietal lobule and sparing of pre- and post-central gyri, the posterior superior temporal gyrus, and the occipital pole. b: Tangle-only dementia brain exhibiting selective atrophy of the hippocampus (arrow) and medial temporal lobe (coronal section at level of mammillary body). c: FTLD (DLDH) brain with marked atrophy of the head of the caudate nucleus (arrow) and marked hydrocephalus (coronal section are level of optic chiasm). d: CBD brain demonstrating circumscribed atrophy of the parasagittal superior frontal gyrus and superior parietal lobule, including the pre- and post-central gyri (arrows). e: FTLD with motor neuron disease brain characterized by atrophy of the pre-central gyrus (arrow) with preservation of the post-central gyrus, while the temporal and frontal lobes also show atrophy. f–i: 3R tauopathy. f: Pick's disease—the dentate fascia shows neuronal loss and inclusions visible with routine histology (H&E). g: Pick's disease—the dentate fascia shows many round Pick bodies by tau immunohistochemistry. h: Pick's disease—white matter glial inclusions (arrow) and threads are seen with tau immunostaining. i: Pick's disease− 2 Pick bodies in brainstem (locus ceruleus) neurons are demonstrated by tau immunostaining. j–p: 4R tauopathies. j: A ballooned neuron from CBD brain immunostained with a neurofilament antibody, but ballooned neurons are also common in Pick's disease. k: An astrocytic plaque in the neocortex of a CBD brain is comprised of a cluster of short stubby tau positive processes surrounding a central clear zone (asterisk). l: Neuropil threads are numerous in both gray and white matter of CBD when detected using tau immunostains. m: Tufted astrocytes (arrow) are common in the motor cortex and the striatum of PSP revealed by tau immunohistochemistry. n: Neuronal inclusions in PSP are typically seen as globose neurofibrillary tangles (NFTs) by tau immunohistochemistry (pontine base). o: Argyrophilic grains are dot-like lesions (arrows) in neurons of the medial temporal lobe and amygdala, and tau immunohistochemistry commonly reveals them in 4R tauopathies, such as this brain from an FTDP-17 patient. p: Coiled bodies are oligodendroglial lesions composed of filamentous tau that are commonly seen using tau immunohistochemistry in several 4R tauopathies, including CBD, PSP, and FTDP-17 as shown here with tau antibodies in the white matter of an FTDP-17 brain. q and r: 3R + 4R tauopathy. Tangle-only disease is a medial temporal lobe tauopathy with many NFTs, but few or no senile plaques. Many of the NFTs are extracellular lesions, and compared with the tau immunostain in (q), the Gallyas silver stain in (r) shows more lesions because phospho-tau epitopes are lost in extracellular NFTs. s–u: FTLD with no insoluble tau. s: Ubiquitin immunostains show clusters of curvilinear processes in the upper cortical lamina in FTLD with MND-type inclusions. t: FTLD with MND inclusions are round ubiquitin-positive, tau-negative inclusions (arrows) that are found in the dentate fascia of the hippocampus. u: Superificial spongiosis in upper cortical lamina (arrows) is the hallmark of FTLD, especially those cases without any distinctive or diagnostic neurodegenerative lesions (H&E).

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