



Case 158

NAME Educational Activities Committee

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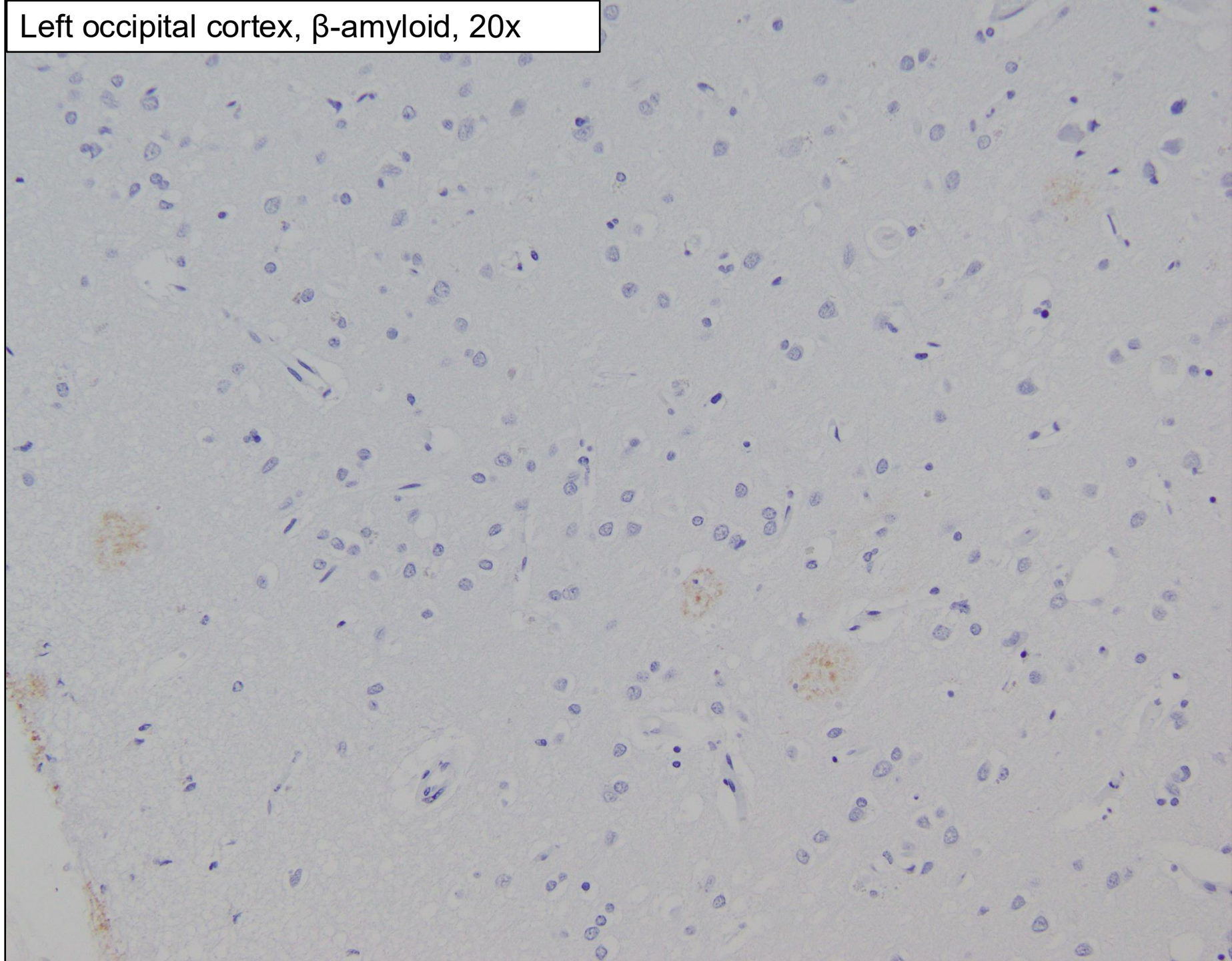
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An 80-year-old female with a past medical history of hypertension, hyperlipidemia, peripheral neuropathy, and depression underwent a brain-only hospital autopsy upon family request. The fresh brain weight was 1,026 grams. Gross examination showed diffuse atrophy, moderate ventricular dilatation, severe non-occlusive atherosclerosis, and moderate arteriolosclerosis. Histologic and immunohistochemical findings are shown in the accompanying images.

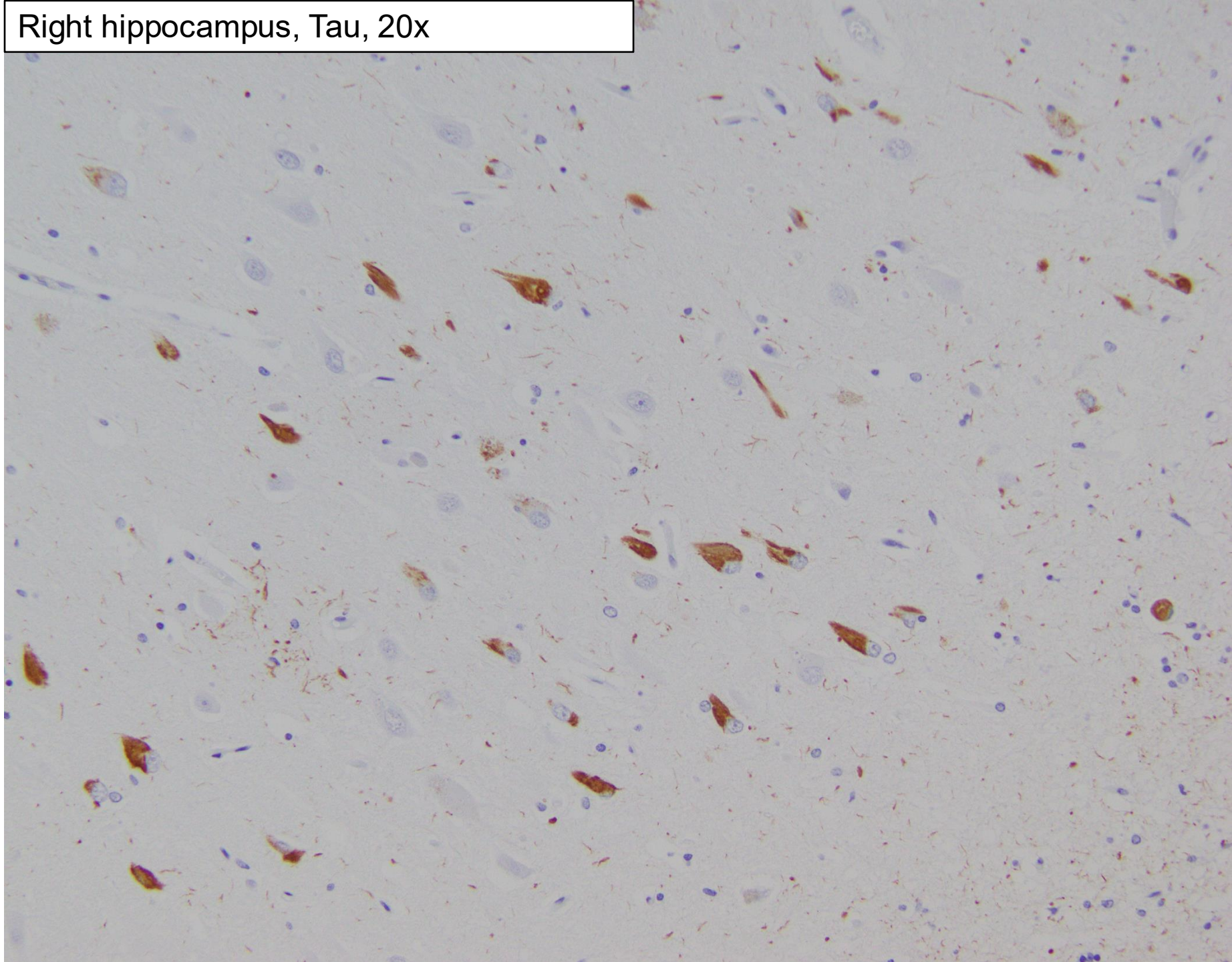
Which premortem history would most strongly support the neuropathologic findings demonstrated in the pictures?

- A. Progressive personality change with disinhibition, compulsive behaviors, and loss of empathy
- B. Recurrent episodes of confusion, somnolence, and flapping tremor accompanied by elevated serum ammonia
- C. Repetitive episodes of head trauma over many years of domestic violence
- D. Several years of progressive memory impairment, increasing dependence on family for self-care, and recurrent visual hallucinations

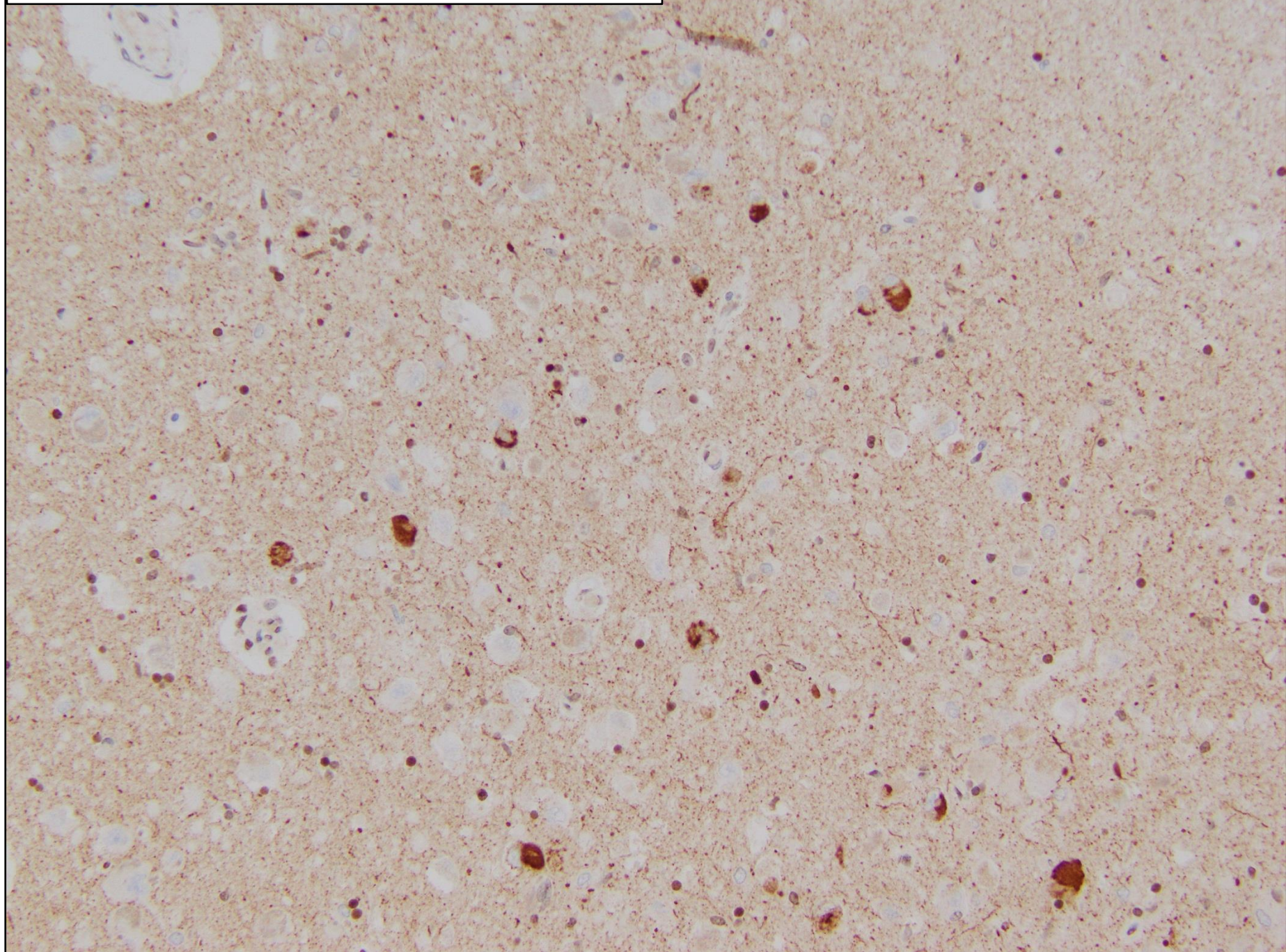
Left occipital cortex, β -amyloid, 20x



Right hippocampus, Tau, 20x



Right hippocampus, α -synuclein, 20x



Answer...

D. Several years of progressive memory impairment, increasing dependence on family for self-care, and recurrent visual hallucinations

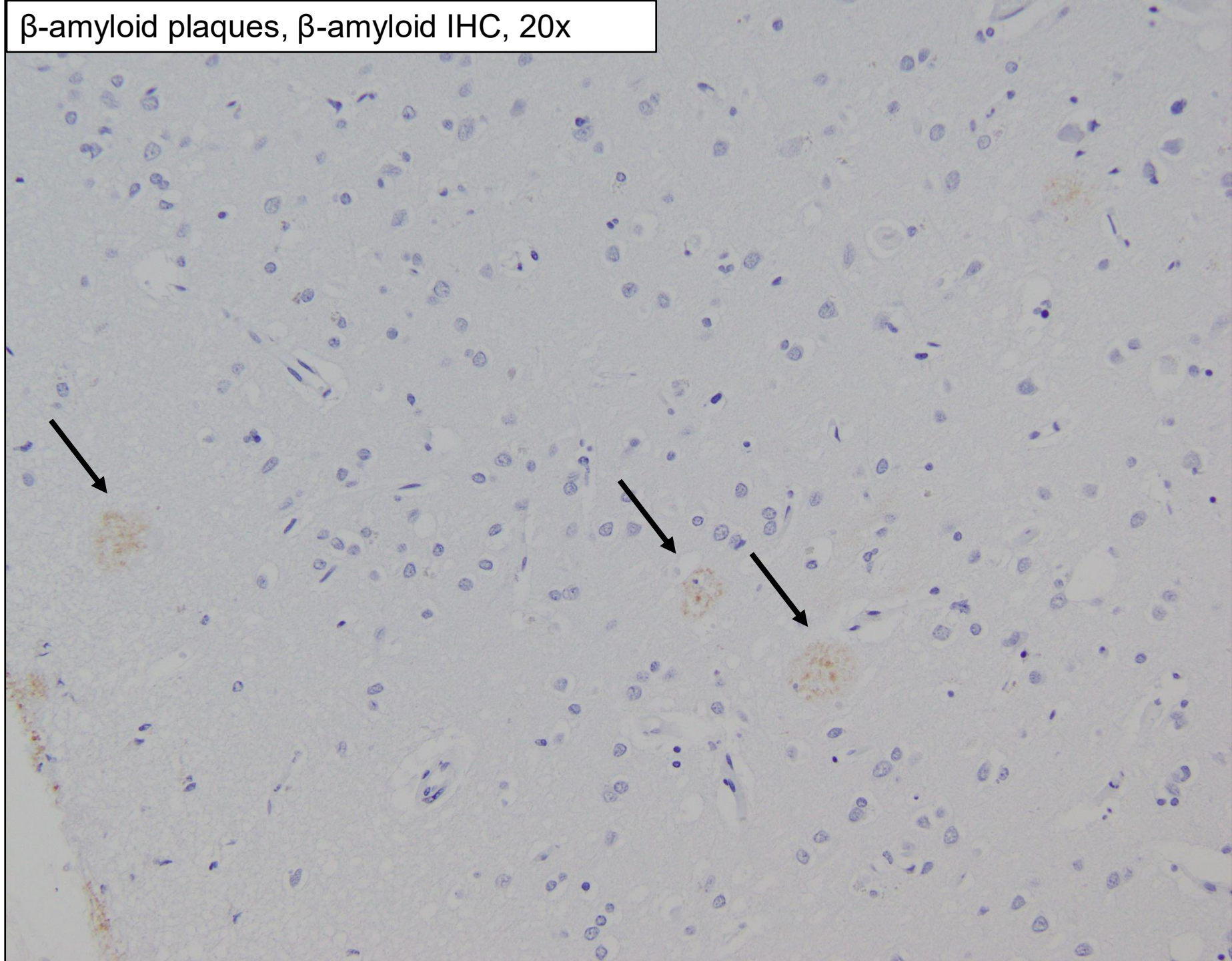
The combination of progressive memory loss, dependence on activities of daily living (ADL), and recurrent visual hallucinations is highly suggestive of Alzheimer's disease neuropathologic change (ADNC) with concomitant Lewy Body Disease (LBD). The diffuse cerebral atrophy (brain weight: 1,026 g) further supports AD as contributing to neurodegeneration.

AD pathological features include amyloid plaques and neurofibrillary tangles, that are depicted in the figures and pointed by the arrows. Amyloid plaques are extracellular deposits of β -amyloid visible on H&E as neuritic or diffuse plaques; pathologic neuritic plaques are associated with dystrophic neurites. Neurofibrillary tangles are intracellular deposits of hyperphosphorylated tau protein - a microtubule-associated protein involved in axoplasmic transport - that appears as pale fibrillar basophilic aggregates on H&E. For staging purposes, both aggregates are better visualized under silver stain (see picture) or immunohistochemical stains for β -amyloid and phosphorylated tau, respectively.

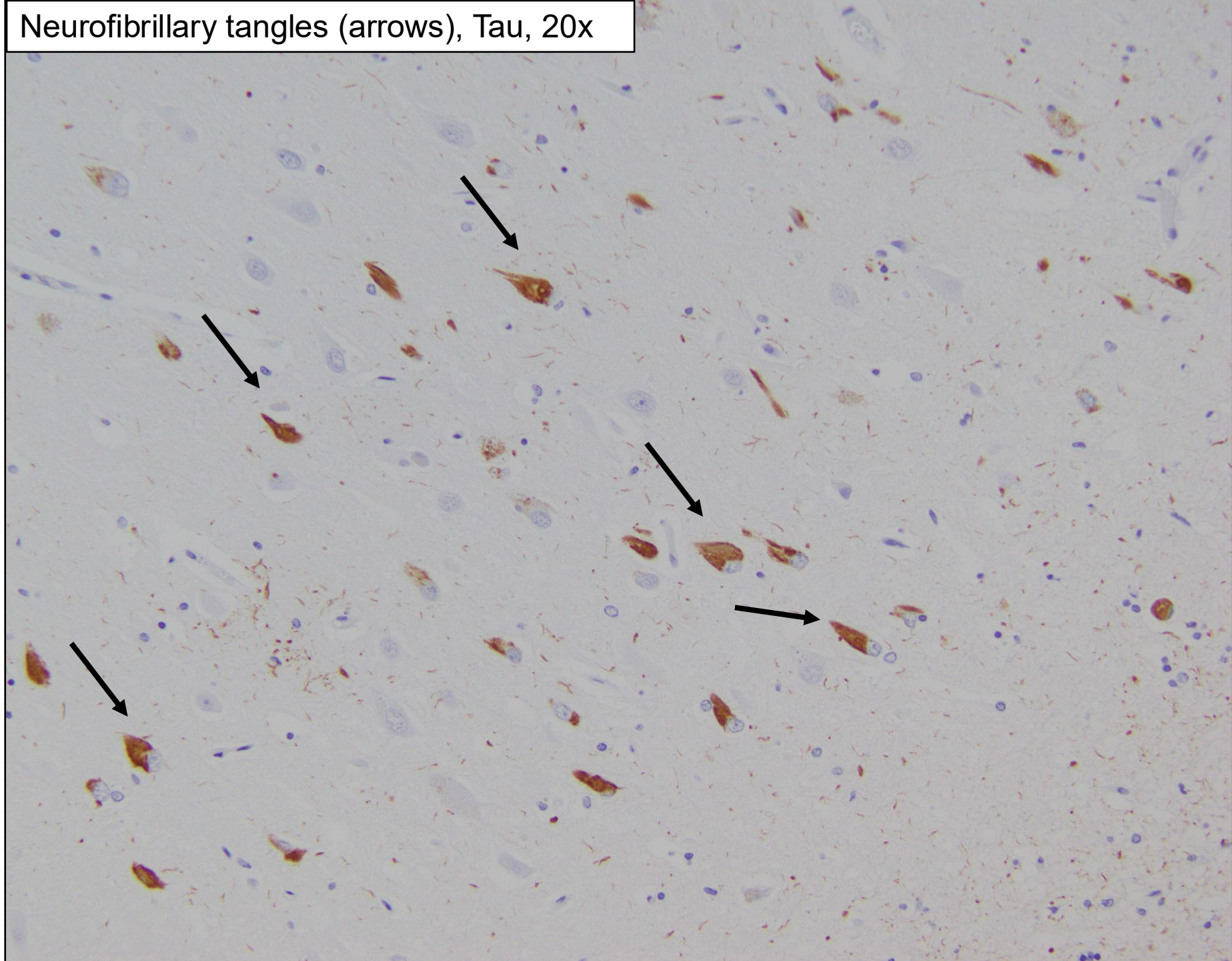
LBD is characterized by Lewy bodies, neuronal cytoplasmic inclusions composed of α -synuclein, that might not be appreciable on H&E but are readily identified with α -synuclein immunohistochemistry (arrows).

AD and LBD are among the most common neurodegenerative disorders in older adults and they frequently coexist, resulting in overlapping clinical manifestations. Although AD typically manifests with memory decline, executive dysfunction and neuropsychiatric symptoms may also be present. Conversely, LBD typically shows executive dysfunction, visual hallucinations, and parkinsonism, but memory impairment is common as the disease progresses.

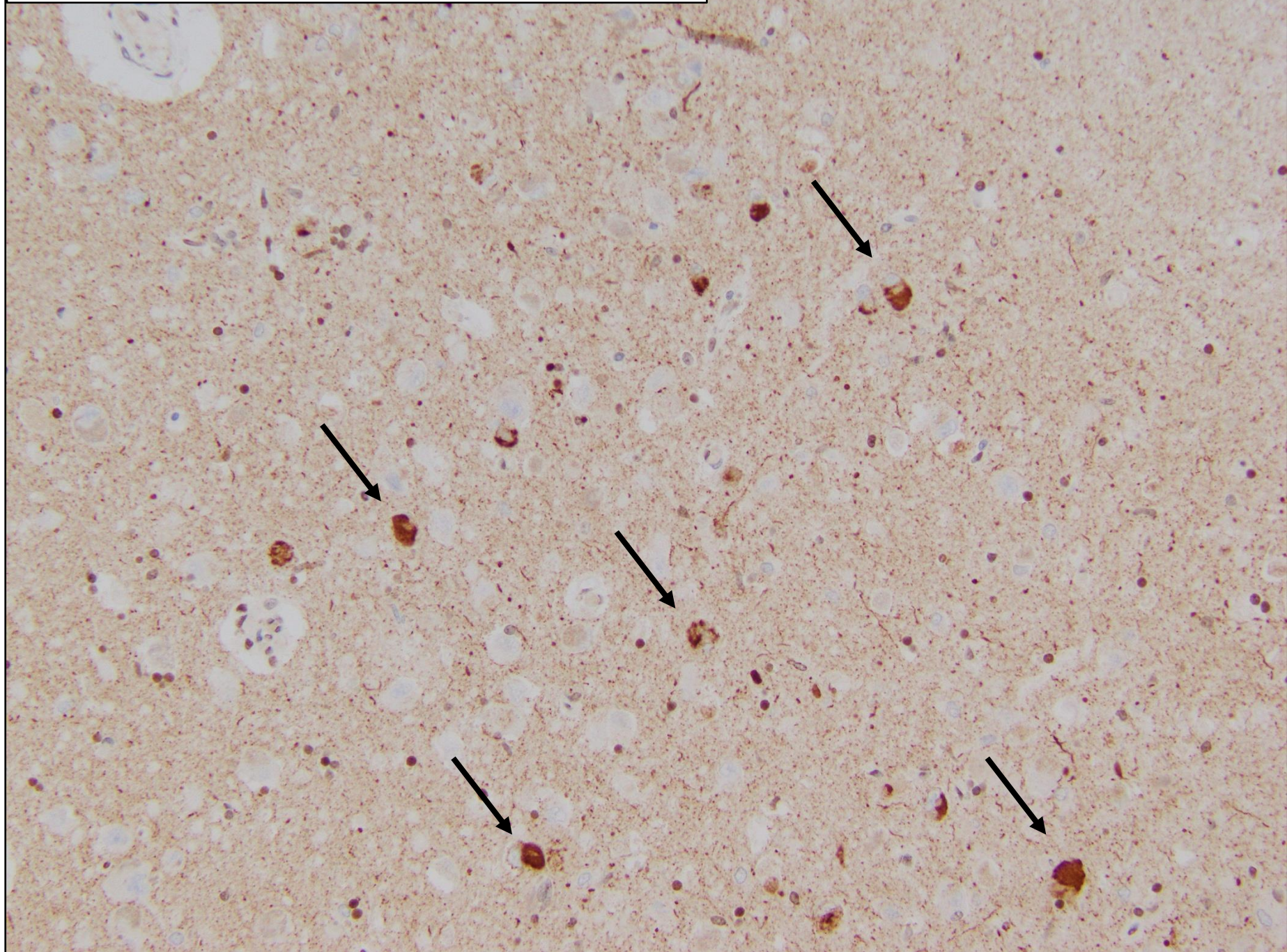
β -amyloid plaques, β -amyloid IHC, 20x

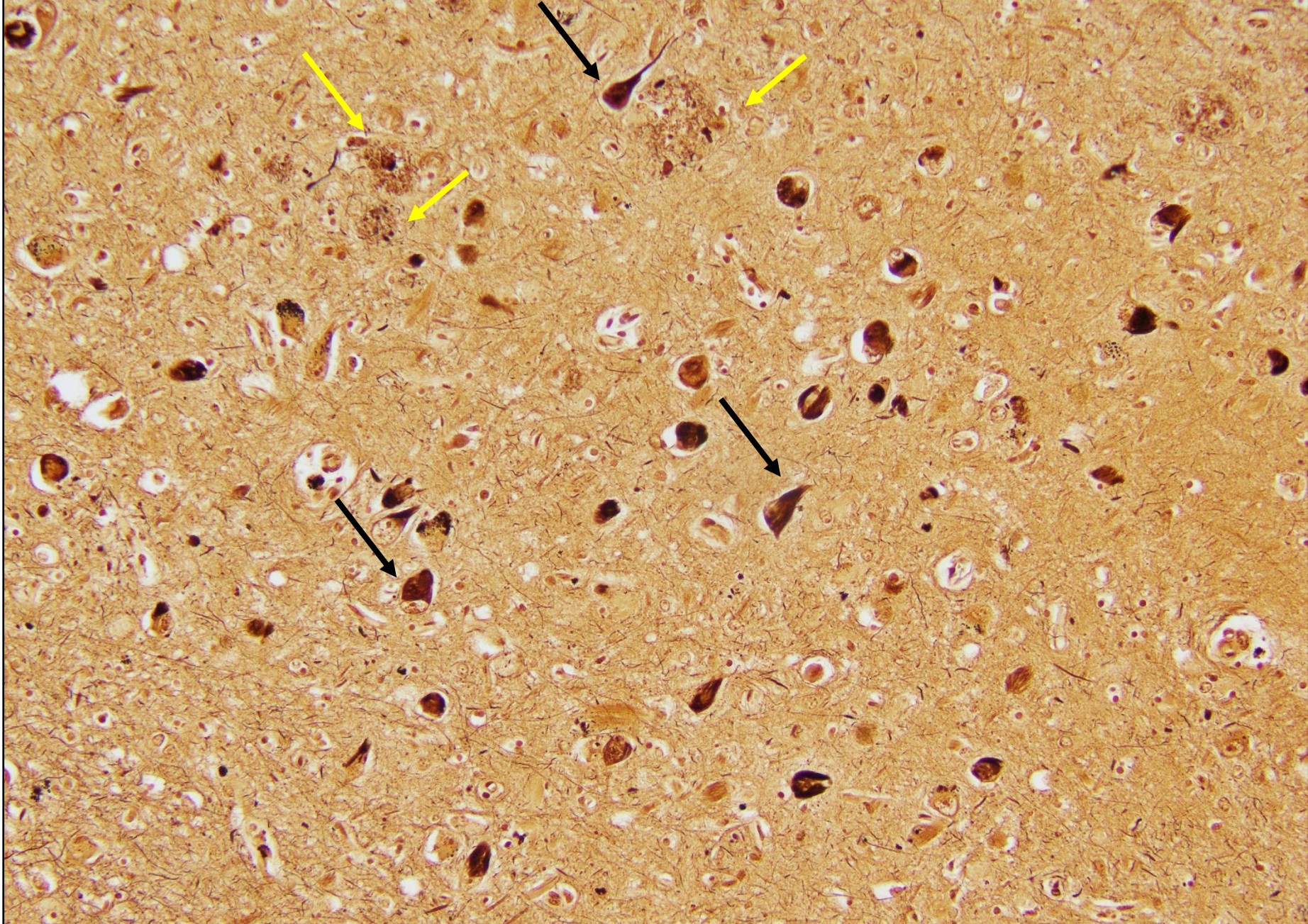


Neurofibrillary tangles (arrows), Tau, 20x



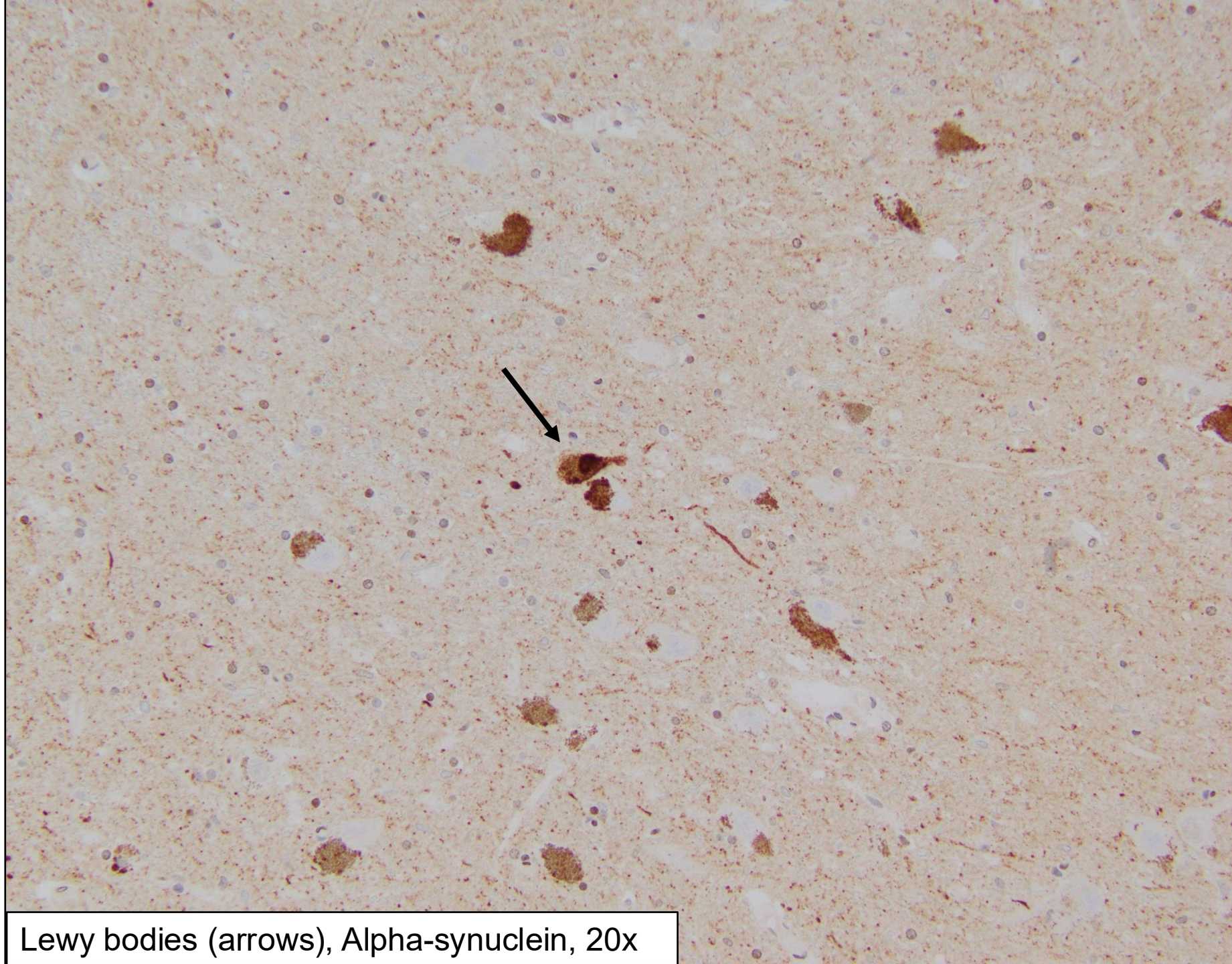
Lewy bodies (arrows), α -synuclein, 20x





Neuritic plaques (yellow arrows) and neurofibrillary tangles (black arrows),
Bielschowski (silver) stain, 20x

NOTE: Lewy bodies in the brainstem (midbrain, arrow) show a slightly different morphology compared to the ones located in the cerebrum.



Lewy bodies (arrows), Alpha-synuclein, 20x

Other responses...

A. Progressive personality change with disinhibition, compulsive behaviors, and loss of empathy

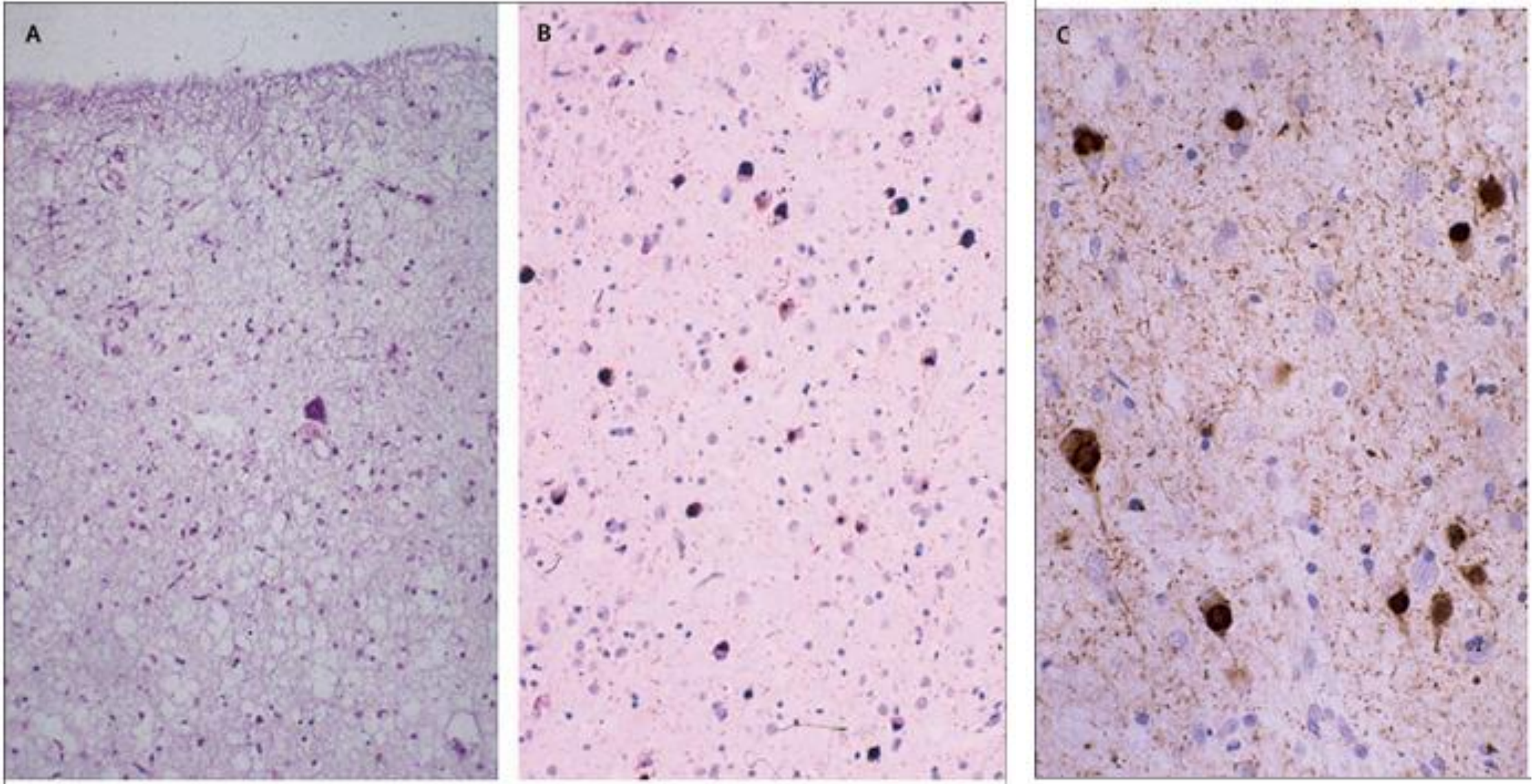
Changes in personality suggest neurodegeneration of the frontal and temporal lobes, as seen in the behavioral variant of frontotemporal dementia (bvFTD). The corresponding neuropathological entity is termed frontotemporal lobar degeneration (FTLD) and is characterized by selective atrophy of the frontal and temporal lobes, in contrast to the more diffuse cerebral atrophy observed in Alzheimer's disease.

Histologically, spongiform changes of the cortical layers (Fig. A) are common, along with characteristic neuronal and glial inclusions. Based on the molecular composition of these inclusions, FTLD can be subclassified into three major groups: FTLD-TDP, with ubiquitinated TAR DNA-binding protein 43 (TDP-43[#]) inclusions in the nuclei and cytoplasm of neurons and glial cells (Fig. B); FTLD-tau, characterized by abnormal neuronal and glial cytoplasmic accumulation of hyperphosphorylated tau (neuronal inclusions called Pick's bodies are characteristic of Pick's disease, Fig. C); and FTLD-FET, characterized by FET proteins^{##} inclusions in the nuclei and cytoplasm of neurons.

DNA/RNA binding protein involved in RNA processing

DNA/RNA binding proteins involved in various aspects of DNA and RNA metabolism





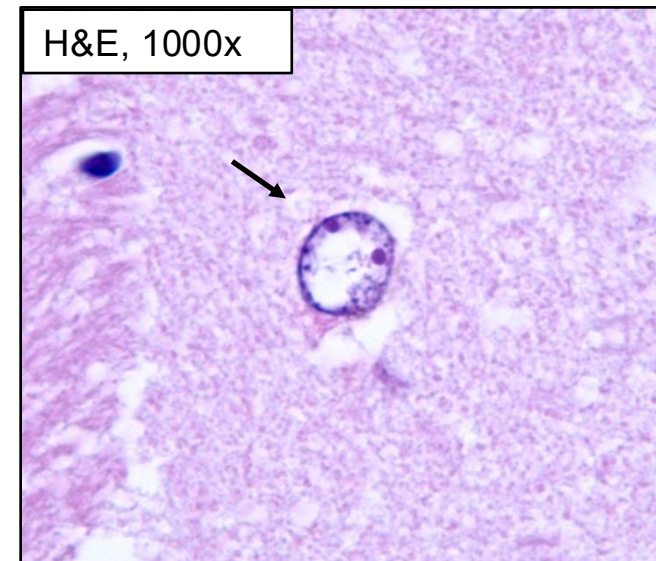
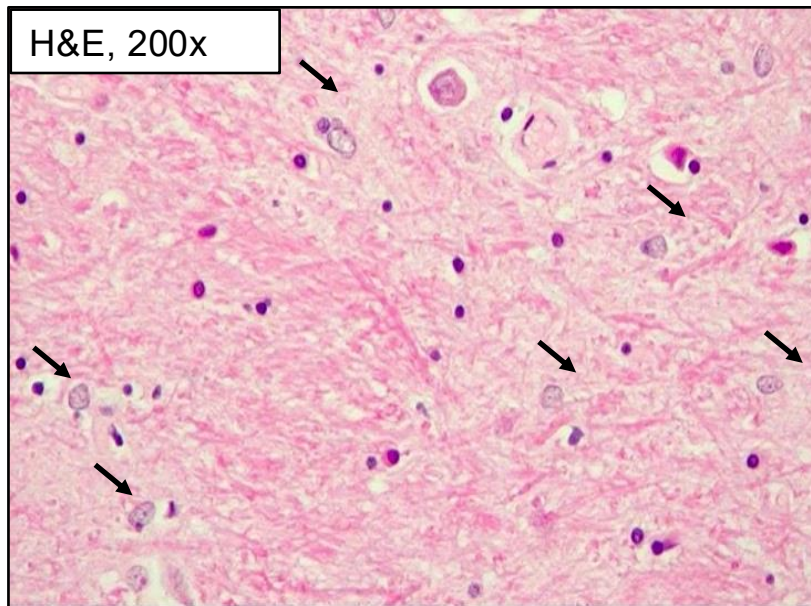
Adapted from: Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol.* 2005 Nov;4(11):771-80. doi: 10.1016/S1474-4422(05)70223-4..

B. Recurrent episodes of confusion, somnolence, and flapping tremor accompanied by elevated serum ammonia

This clinical scenario is suggestive of hepatic encephalopathy, a spectrum of neurocognitive abnormalities that occurs in patients with acute or chronic liver disease or portosystemic shunting. The elevated ammonia levels suggest underlying liver disease, and amyloid plaques/neurofibrillary tangles would not be expected.

A characteristic finding is (represented by the cells indicated by the arrows) Alzheimer type II astrocytes (AA II), which, despite their name, are unrelated to Alzheimer's disease. AA II astrocytes exhibit a spectrum of nuclear changes, ranging from slight nuclear enlargement with chromatin loosening to a completely clear ("empty") nucleus with a well-defined nuclear membrane and peripheral dot-like chromatin condensation (arrows). They frequently occur in pairs and may occasionally form triplets.

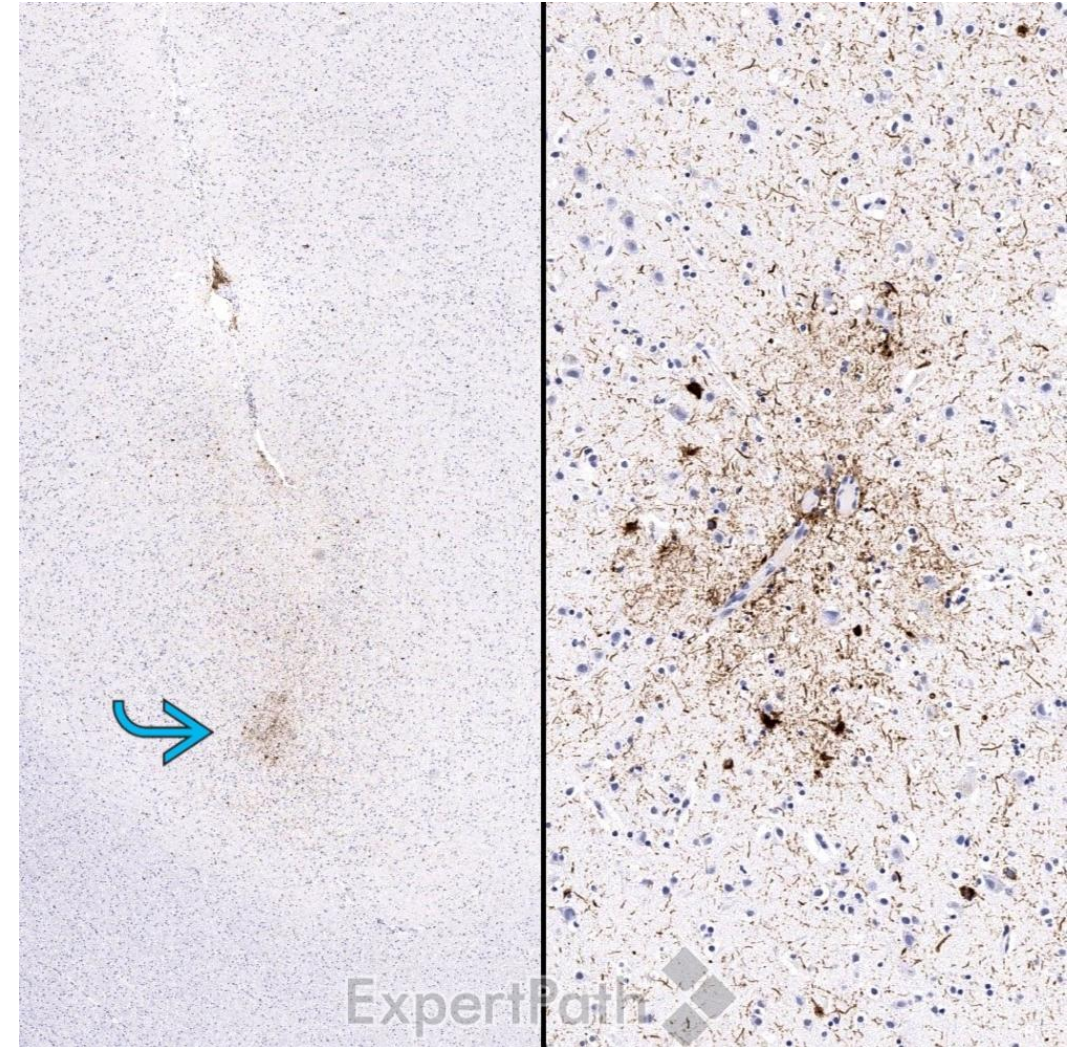
p62 has recently been proposed as an immunohistochemical marker for the identification of AA II astrocytes.



C. Repetitive episodes of head trauma over many years of domestic violence

A history of repetitive head impacts is characteristic of chronic traumatic encephalopathy (CTE). CTE has been frequently reported in individuals participating in contact sports, including rugby and football, although any history of repeated head trauma should raise suspicion. CTE is a neuropathological diagnosis.

Its pathognomonic lesion consists of neuronal accumulation of phosphorylated tau (p-tau) at the depths of cortical sulci (left image, arrow), typically surrounding small blood vessels (right image) in the deeper cortical layers and not confined to the subpial or superficial regions of the sulcus. In contrast, the p-tau pathology of Alzheimer's disease neuropathologic change (ADNC) is distributed more uniformly across gyri and sulci. However, in advanced-stage CTE, the widespread cortical distribution of p-tau may resemble that seen in ADNC.



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