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Alzheimer's Disease Neuropathology May Not Predict Functional Impairment in HIV: A Report of Two Individuals

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Abstract

With aging of HIV populations, there is concern that Alzheimer's disease (AD) may become prevalent and difficult to distinguish from HIV-Associated Neurocognitive Disorders. To date, there are no reports documenting histologically verified Alzheimer's neuropathology in individuals with HIV and dementia. Herein, we report two antiretroviral-treated, virally suppressed, HIV-infected individuals autopsied by the Manhattan HIV Brain Bank. Subject A presented to study at 52 years, already dependent in instrumental activities of daily living (ADLs), with severe cognitive impairment inclusive of learning and memory dysfunction. Her history was significant for educational disability and head trauma. She had rapid cognitive decline, and by death at age 59, was bed-bound, incontinent, and non-communicative. At autopsy, she exhibited severe AD neuropathologic change (NIA-AA score A3B3C3) and age-related tau astroglial pathology (ARTAG). She was homozygous for *APOE* $\epsilon 3/\epsilon 3$. No HIV DNA was detected in frontal lobe by nested polymerase chain reaction. Subject B was a community dwelling 81-year-old woman who experienced sudden death by pulmonary embolus. Prior to death, she was fully functional, living independently, and managing all ADLs. At autopsy, she displayed moderate amyloid and severe tau AD neuropathologic changes (A2B3C2), ARTAG, and cerebral congophilic angiopathy. She

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was an *APOE* ε3/ε4 heterozygote, and HIV DNA, but not RNA, was detected in frontal lobe, despite 20 years of therapy-induced viral suppression. We conclude that in the setting of HIV, AD neuropathology may occur with or without symptomatic cognitive dysfunction; as with seronegative individuals, there are likely to be complex factors in the generation of clinically relevant impairments.

Keywords

Alzheimer's disease; HIV; age-related tau astrogliopathy

Introduction

Alzheimer's disease (AD) is a highly prevalent and progressive dementing disorder that encompasses sporadic and familial subtypes varying in their typical age of onset and genetic associations. Common to these subtypes are variable combinations of three histopathologic features: neurofibrillary tangles, neuritic plaques, and amyloid deposition. In 2012, an expert consensus panel updated the National Institute on Aging - Alzheimer's Association (NIA-AA) guidelines for assessing these neuropathologies, arriving at an "ABC" scoring system based on the prior classifications of Braak and Braak, Thal, and the Consortium to Establish a Registry for AD (CERAD) (Montine, 2012). The guidelines entailed independent scoring of amyloid (A), neurofibrillary tangles (B), and neuritic plaques (C), with each category graded on a scale of 0–3. However, even with these explicit and well-documented guidelines, the relationship between histopathology and cognitive/behavioral abnormality remains problematic. It is well recognized that AD neuropathology can be identified in a spectrum of clinical states, including individuals who are cognitively normal, sub-clinically impaired, and those with mild cognitive impairment or advanced dementia (McKhann, 2011; Montine, 2012; Davis, 1999).

The variable relationship between neuropathology and functional deficit has led to deeper analysis; some focused on the type, degree, and distribution of neuropathology as a means of identifying changes associated with clinical deficit; others examining co-factors such as lack of cognitive reserve, vascular disease, and head trauma, in generating clinical disease (SantaCruz, 2011; Serrano-Pozo, 2013; Nelson, 2010; Crystal, 2014; Gupta, 2016; Serra, 2015). One research focus has been on the pathogenetic role of infection and neuroinflammation (Mosher, 2014; Heneka, 2015; Piirainen, 2017). With use of combined antiretroviral therapies (cART) and the aging of HIV-infected individuals into decades in which neurodegenerative disorders occur, there is concern that the chronic immune stimulus effectuated by persistent HIV will constitute a co-morbidity increasing risk for AD. This concern is difficult to resolve on a clinical basis, as there remains a high burden of HIV-associated neurocognitive disorders (HAND) in cART era populations (Heaton, 2010; Heaton, 2011). Accordingly, studies to evaluate AD-related biomarkers in HIV populations have been undertaken, albeit at mean ages (late 30s and 40s) atypical for initial manifestations of sporadic AD (Ances, 2012; Clifford, 2009; Gisslen, 2009). Perhaps unsurprisingly, many of these younger populations do not resemble those with typical AD.

In the absence of validated peripheral markers to distinguish HAND and early onset AD, evaluation of brain tissues, through positron emission tomography (PET)-ligand imaging of the living or direct neuropathologic observation of the deceased, may aid in the development of tools to resolve the etiology of cognitive impairment in individuals with HIV. A single case report of an HIV-infected individual with progressive mild dementia, low A β 42/tau index in the cerebrospinal fluid (CSF), and brain amyloid detected on PET has been published; while findings were consistent with both HAND and AD, neuropathologic confirmation was not available (Turner, 2016). Herein, we report two cART-treated, virally-suppressed, HIV-infected individuals found at autopsy to display AD neuropathologic change, inclusive of neurofibrillary tangles, neuritic plaques, and amyloid deposition. We describe their cognitive/functional status, significant co-morbidities, selected genetic analysis, and neuropathology as a means of exploring factors relevant to the generation of clinically manifest AD in individuals with chronic, cART-treated HIV.

Methods

Patients:

The subjects of this report were autopsied by the Manhattan HIV Brain Bank (MHBB) at the Mount Sinai Hospital (MSH), NY, NY. MHBB, member of the National NeuroAIDS Tissue Consortium (NNTC), is part of a research resource supporting brain banks for the conduct of neuroHIV research (Morgello, 2001). MHBB performs autopsies on cognitively characterized individuals in its longitudinal study, as well as on those in clinical care at MSH. Subject A had participated in the MHBB study, with consent provided by her primary next of kin; this study is monitored and approved by the institutional review board of the Icahn School of Medicine at Mount Sinai (ISMMS). Study subjects undergo neurologic, neuropsychologic, and psychiatric evaluations as described previously (Ryan, 2004). The neuropsychologic test battery examines six putative cognitive domains: learning; memory; abstraction/executive functioning; speed of information processing; verbal fluency; and motor (Woods, et al., 2004). For subject B, next of kin provided autopsy consent via MSH standard protocol, which stipulates diagnostic, research and educational purposes for the evaluation. While this subject did not undergo cognitive testing (there was no clinical indication for assessment), her functional status was obtained by review of the medical record and interview of her primary care providers.

Neuropathologic and molecular/genetic assessment: Neuropathologic procedures for the NNTC have been published previously (Morgello, 2001). Briefly, at autopsy the brain is bisected; half is frozen, and half fixed in formalin for routine histology. At MHBB, a total of 57 sections are obtained from brain and spinal cord, and stained with hematoxylin and eosin. For the current study, the following histochemical and immunohistochemical stains were performed on sections of hippocampus, frontal, temporal, parietal and occipital cortex, basal ganglia, amygdala/entorhinal cortex, and cerebellum: Bielschowsky silver stain, immunohistochemistry for hyperphosphorylated tau (AT8 mouse monoclonal antibody, Thermo Scientific), β -amyloid (6F/3D mouse monoclonal antibody, Dako Corporation), activated macrophage/microglial cell marker CD68 (KP1 mouse monoclonal antibody, Dako Corporation), and HIV p24 protein (Kal-1 mouse monoclonal antibody, Dako Corporation).

Limited regional staining was also done for α -synuclein (Clone KM51 mouse monoclonal antibody, Novocastra), with no evidence of Lewy body pathology. Immunohistochemistry was performed with diaminobenzidine chromogen and hematoxylin counter-stain. Slides were examined by two board-certified diagnostic neuropathologists (SM and JC).

ApoE genotyping was done on DNA extracted from peripheral blood mononuclear cells or brain tissue with the Qiagen DNeasy blood and tissue kit (Qiagen, Venio, The Netherlands). Taqman SNP genotyping assays targeting rs429358 and rs7412 were used to determine *APOE* alleles (Applied Biosystems, Foster City, CA). Assay for HIV provirus was performed on DNA extracted with the DNeasy kit from brain tissues; for each subject, a minimum of two regions within a 1.5 cm area of anterior frontal lobe were used, and each DNA extract tested individually. Nested polymerase chain reaction (PCR) to detect HIV *gag* and *pol* was performed using 200 nM primers as described in (Albert, 1990) (primer sets JA4 through JA7 for *gag*, and JA17 through JA20 for *pol*), in Platinum PCR SuperMix High Fidelity (Invitrogen, Carlsbad, CA) for inner and outer *pol* and inner *gag* primers, and Radiant GC-long hot start master mix (Alkali Scientific, Fort Lauderdale, FL) for outer *gag* primers. Reaction products were electrophoresed on 3% NuSieve, 1% agarose gels; bands excised and purified with QIAquick gel extraction kit; and identity confirmed via Sanger sequencing (Genewiz Corporation, South Plainfield, NJ) using forward and reverse nested primers and alignment through NCBI BLAST; all reaction products had 100% coverage with deposited HIV-1 sequences. Anterior frontal lobe RNA was extracted with Qiagen RNeasy mini kit, and reverse transcription performed using qScript cDNA supermix (Quanta Biosciences, Gaithersburg, MD). Nested reactions for HIV *pol* were then performed. Positive controls included brain tissue with HIV encephalitis; negative controls included HIV negative brain tissue and reactions conducted in the absence of nucleic acid template. Integrity of DNA and RNA was assured through PCR amplification of cellular sequences (the single copy amelogenin gene for DNA (Gilbert MTP, 2007) and GAPDH for RNA (Konomi N, 2002)).

Patient A was also represented on an Infinium HumanCore Exome chip as part of ongoing research by one of the authors (K01DA035725, to MJ). Single nucleotide polymorphisms in the presenilin (PSEN1 and PSEN2) and amyloid precursor protein (APP) genes represented on this platform were examined.

Results

Subject A was a 52-year-old Caucasian woman who presented to MHBB in the company of her daughter; both were concerned about decline in the subject's cognitive function. She had been diagnosed with sexually-acquired HIV infection at age 42. Other medical disorders included osteopetrosis and hip fracture, hyperlipidemia, cystic breasts, vitamin B-12 deficiency, remote hepatitis B, and smoking. She was adherent to Atripla, and 5 plasma HIV loads in the last two years of life ranged from undetectable to 114 copies/ml.

The subject evidenced multiple cognitive risk factors: indicators of childhood abuse/neglect/malnutrition, closed head injury secondary to domestic violence, and special education classes, with a 3rd grade reading level on the Wide Range Achievement Test –3. Family

history was significant for her mother evidencing severe behavioral disturbances (reported diagnoses of schizophrenia and bipolar disorder), with functional decline from full-time employment to incapacitation and death around age 50. The subject's sister was alive in her early 60s and experiencing "memory problems."

Behaviorally, the subject was friendly, cooperative and anxious about her performance on cognitive tests. Except for mild anxiety, there were no signs of psychiatric disturbance based upon observation, medical record and clinical interview. She lived with family members and was reported to be dependent for most activities of daily living, although she provided childcare to young grandchildren and enjoyed playing card games.

Secondary to significant comprehension difficulties, the subject completed an abbreviated cognitive battery, and required multiple repetitions of test instructions. The assessment was notable for severely advanced global cognitive impairment. Memory impairment was profound. She was unable to recall remote or recent personal history details, including her birth date and the names of her children. On a list learning task (HVLT-R), she received the lowest possible score, manifesting a significant recency effect. Recognition memory was at chance level with marked false positive errors. Performance on a test of simple psychomotor speed (TMT-A) was exceptionally slow and effortful. At a 6-month follow up evaluation, she was even more impaired and unable to complete any cognitive tests. With progressive deterioration she was institutionalized, and by the time of her death 6 3/4 years after study presentation, was bed-bound, mute and incontinent, in advanced stages of dementia. Autopsy permission was restricted to examination of brain and spinal cord.

The brain weighed 880 grams and displayed significant cortical atrophy, most pronounced in frontal and temporal regions (figure 1). Mild flattening of the heads of the caudate nuclei, and significant ventricular dilation, most pronounced in temporal regions, were also present. Microscopically, severe AD neuropathologic change A3B3C3 was demonstrated, with regionally numerous neurofibrillary tangles and neuritic plaques with and without amyloid cores. Immunohistochemical stains for phosphorylated tau protein confirmed the presence of plaques and tangles, additionally highlighting numerous pre-tangles; in some temporal regions (entorhinal cortex and amygdala), virtually all neurons contained phosphorylated tau. Dense bands of phosphorylated tau immunoreactivity were seen in all gray matter regions, reflecting diffuse neuritic accumulations outside of plaques and neuronal perikarya. Phosphorylated tau was also present in white matter astrocytes in all supratentorial locations examined, and in scattered astrocytes in deep cerebral gray matter and brainstem. This age-related tau astrogliopathy (ARTAG) was characterized by thornshaped, granular, and "fuzzy" astrocytes. There was no evidence of a pattern characteristic of chronic traumatic encephalopathy (McKee AC, 2016). β -amyloid was plaque-associated, with no evidence of amyloid angiopathy. Immunostains for α -synuclein were negative. Numerous CD68 immunoreactive microglia/macrophages were present in all brain regions, in perivascular locations, plaque-like aggregates, as well as diffusely infiltrative patterns. Microglial nodules characteristic of viral disease were not present. HIV p24 immunohistochemistry was negative, and no HIV DNA or RNA was detected in frontal lobe tissues. Genetic analysis revealed that the patient was an *APOE* $\epsilon 3/\epsilon 3$ homozygote. All loci for *PSEN2*, and *APP* on the Infinium exome array were wild type (supplemental table 1). A single rare variant was

noted in PSEN1 at rs2272585, where the subject was a heterozygote. This intron SNV is of unclear significance, with no reports in dbSNP. Resources to sequence these genes were not available for the purposes of this report.

Subject B was an 81 year-old AA woman who was living independently, managing all her ADLs, with regular exercise as part of her weekly regimen. Her diagnosis of HIV was made 20 years prior to demise, when she presented with a CD4 nadir of 208 cells/mm³ and a viral load of 54,700 copies/ml. Her risk factor was sexual exposure, with no history of smoking or illicit substance use. Subsequent to diagnosis, she was provided continuous ARV therapy for the remainder of her life, with varying regimens inclusive of crixivan, zidovudine, lamivudine, combivir, and sustiva; she was compliant with atipla for the last 10 years. A total of 56 viral loads were documented in her medical record over the 20 years, with the last occurring 3 months prior to death; all were undetectable with the exception of one value of 98 copies/ml occurring 9 years prior to demise. Her last CD4 count 3 months prior to demise was 1115. Other significant medical illnesses included: hypertension; hypertensive heart disease with angina; peripheral vascular disease with mild left carotid artery stenosis (30% narrowing); hyperlipidemia; diverticulosis; glaucoma; total abdominal hysterectomy; and previous pulmonary embolism. On the day of death she had a syncopal episode with shortness of breath and chest pain. She arrested, and could not be resuscitated. A saddle pulmonary embolus was the cause of death. Other systemic autopsy findings included moderate coronary and systemic atherosclerosis, cardiomegaly, nephrosclerosis, and diverticular disease.

The brain weighed 1050 grams, with mild cortical atrophy in frontal and parietal lobes. It was otherwise grossly unremarkable. Microscopically, intermediate AD neuropathologic change A2B3C2 was demonstrated. Phosphorylated tau immunostaining displayed a gradient of neuronal and neuritic accumulation, most prominent in medial temporal structures and to lesser degrees in neocortex, deep cerebral gray matter and brainstem. Age-related tau astrogliopathy (ARTAG) was also seen, with moderate numbers of predominantly temporal lobe white matter thorn-shaped astrocytes, and scattered phosphorylated tau-expressing astrocytes in basal ganglia and capsular white matter, basal forebrain, and subpial temporal cortical locations. Occasional Hirano bodies and granulovacuolar degeneration were noted in hippocampus. β -amyloid deposition was both plaque-associated, as well as in cortical and leptomeningeal arterioles. Immunostains for α -synuclein were negative. CD68 immunoreactivity was generally moderate and greater in white matter than gray, but also associated with neuritic plaques; microglial nodules characteristic of viral infection were not identified. Immunohistochemical stains for HIV p24 antigen were negative, as was nested RT-PCR for HIV RNA. HIV DNA was detected in two samples of anterior frontal lobe by nested PCRs for *gag* and *pol*. The patient was an *APOE* ϵ 3/ ϵ 4 heterozygote.

Discussion

Herein we describe two HIV-infected women with many years of cART-induced viral suppression who displayed AD neuropathology and no evidence of active HIV replication in brain. Subject A's clinical presentation was consistent with familial, early onset AD (EOAD), with histories of significant maternal and sibling mid-life cognitive dysfunction.

She was wild type for all PSEN2 and APP SNPs represented in an exome array, and had one rare intronic SNV in PSEN1 of unclear clinical significance; we were unable to completely sequence these genes and cannot rule out idiosyncratic familial mutations with known clinical significance. Importantly, this subject also had other risk factors for cognitive dysfunction, inclusive of childhood neglect, low literacy, and head trauma. Subject B did not undergo neuropsychologic testing, nor was there information in the medical record regarding cognitive risk factors or occupational status prior to HIV diagnosis. However, she was independent in ADLs and without any mention of cognitive difficulties in a record documenting self-care for 20 years. Thus, it could reasonably be inferred that she did not have clinically manifest AD; she was functionally normal, although we cannot rule out the possibility that formalized cognitive testing may have revealed sub-syndromic deficits. Furthermore, in this subject, despite 20 years of consistent, cART-induced viral suppression, HIV DNA persisted in her frontal lobe. Together these individuals represent a spectrum of the AD continuum: one with severe neuropathology and early onset disease; the other with no indications of functional incapacitation by an advanced age, and moderate neuropathology. Importantly, there was no indication in either patient that the histologic manifestations of AD neuropathology were in any way altered by their long histories of cART-controlled HIV infection, and counter-intuitively, persistent brain HIV DNA was only detected in the subject without functional impairment.

The generation of clinically significant cognitive deficits, whether in the setting of HIV infection or neurodegenerative disorders, is a complex phenomenon that may defy linear relationship to discrete neuropathology. In cART-era HIV, when neuropathology has been directly examined, the histologic correlates of HAND have been minimal, non-diagnostic changes, or Alzheimer's type 2 gliosis; the latter raising the possibility of metabolic contributions to cognitive impairment, as it is a pathology typically associated with hepatic dysfunction (Everall, 2009). Conversely, in age-related neurodegenerative disorders, while severe AD neuropathology is generally acknowledged as a dementia substrate, mild and moderate forms of the same histopathology can be seen in individuals who are cognitively normal by rigorous neuropsychologic testing (McKhann, 2011; Montine, 2012; Davis, 1999). Thus, while traditional neuropathology is an important means to classify disease and can be used as an indicator of potential pathogenetic mechanism, it may be lacking as a means to define the boundaries of relevant or irrelevant sub-clinical abnormality. The patients presented herein raise the issue of how to appropriately define a patient population in need of disease-specific intervention. For AD, there has been extensive focus on the role of β -amyloid PET as a diagnostic tool for this clinical resolution (Ossenkoppele, 2015; Donohue, 2017; Jansen, 2015). The likelihood of detecting brain amyloid with this modality is associated with age and *APOE* status, and in individuals with dementia, differential rates of deposition in the context of these factors are seen; thus, it is thought to have clinical utility for early-onset dementia and AD dementia in individuals who have noncarrier *APOE* ϵ 4 status older than 70 years of age (Ossenkoppele, 2015). The detection of brain amyloid in cognitive normals raises the concept of AD without dementia, and whether it portends eventual cognitive decline, and over what interval of time, is an active topic of investigation (Donohue, 2017; Visser, 2017).

How does the AD literature apply to aging individuals with HIV? The subjects reported herein provide no evidence for a significant role of HIV in their primary neuropathologies. Subject A raises the question of what measures should be routinely taken to resolve the pathogenesis of mid-life cognitive impairments in the setting of cART-controlled HIV, particularly as there is such prevalent, mild dysfunction that for the most part does not progress over many years of observation (Heaton, et al., 2015). However, for progressive dementias in mid-life individuals with HIV, imaging modalities and cerebrospinal fluid (CSF) biomarker studies to identify amyloid and phosphorylated tau should be considered to help resolve whether EOAD can be entertained in the differential diagnosis.

Another aspect of the neuropathology presented herein is the concurrent presence of ARTAG in both individuals. This neuropathology is frequently encountered in temporal lobe of older individuals, and thus, its presence in an 81-year-old is within the boundaries of normal aging (Schultz, 2004; Lace, 2012). The significance of its more diffuse distribution in an individual with EOAD is unclear, although severe AD neuropathology (as seen in patient A) is associated with increased risk for pan-lobar ARTAG pathology (Kovacs, 2017). Given the relatively high frequency of ARTAG in HIV-negative aging populations, its presence in the setting of AD neuropathology in two HIV-positive individuals does not provide a basis for commenting on tauopathy-HIV synergies; larger numbers of brain autopsies will be required to resolve its prevalence at all ages in HIV. However, it is important to note that ARTAG is thought to reflect abnormalities at brain-fluid interfaces, such as blood-brain barrier (BBB) abnormalities; surveillance for increased prevalence of this pathology in HIV is therefore warranted (Kovacs, 2017).

Finally, how do these patients provide insight into the intersection of HIV and AD neuropathogenesis in the setting of cART-induced viral suppression? Evidence of brain HIV replication was absent in these individuals, consistent with their long-term viral suppression and absence of CNS escape; in the significantly impaired subject A, we did not even detect persistent viral DNA. As a caveat, we undertook circumscribed brain sampling, as these tissues are part of our research resource for other investigators; importantly, we did not examine basal ganglia, a “hot spot” for HIV. Nevertheless, counter-intuitively, HIV DNA was detected in the functionally intact subject, despite continuous cART-induced viral suppression for a period of 20 years after initial diagnosis. Together, these patients suggest that with cART-control, persistent brain virus may be clinically irrelevant in individuals with AD neuropathology, although a role of persistent HIV in stimulating histopathology (as opposed to clinical deficit) is possible. There is literature describing HIV-associated brain amyloid deposition, albeit controversial as to whether it is any greater than in age-matched controls, particularly when controlled for APOE status (Green, 2005; Achim, 2009; Solomon, 2017; Rempel, 2005; Soontornniyomkij V, 2012). Furthermore, there is variable association with cognitive status. In an NNTC study, age and APOE status were the major predictors of cortical amyloid deposition (as is the case in HIV negatives), and amyloid served as a predictor of HAND only in $\epsilon 4$ carriers (Soontornniyomkij V, 2012). The cARTera literature on HIV-associated deposition of phosphorylated tau is less robust; to our knowledge a single study has shown increased hippocampal expression compared with age-matched controls, again, in the absence of cognitive correlates (Anthony, 2006). A single HIV-infected individual with histologically-verified Alzheimer’s neuropathology is cited in

the literature, again without analysis of pre-mortem cognitive status (Solomon, 2017). The two patients described herein represent the first analysis of HIV-associated AD neuropathology vis-a-vis clinical manifestations, and they underscore that histology is unfortunately not a gold standard for prediction of cognitive function, and that furthermore, on a case-by-case basis without rigorous control of HIV negatives with similar cognitive comorbidities, these individuals cannot be used to support or detract from speculation that HIV in some manner potentiates AD.

In summary, these patients demonstrate the need to encompass both behavioral and histopathologic or biomarker analyses in studies of potential HIV-aging interactions, as thresholds for significant cognitive impairment may defy quantitative categorization of the three primary lesions (i.e., amyloid, neurofibrillary tangles, neuritic plaques) constituting AD neuropathology. It may be that mid-life work up for HIV-associated AD neuropathology through β -amyloid PET imaging will have greatest utility in those without APOE risk, as with HIV negatives. However, further analysis will be required to determine whether the kinetics of amyloid deposition in individuals with long term viral suppression are similar to that seen in the absence of HIV, and whether HIV-associated cognitive trajectories will have similar relationship to AD neuropathologies defined by these imaging modalities, or will require altered approaches to commonly used nosologies for the classification of age-related neurodegenerative disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest:

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Figure 1.

Severe Alzheimer's disease neuropathological changes in a demented 52-year-old woman with long-term viral suppression (subject A). Panels A and B: Severe atrophy, seen on lateral view of the hemi-sectioned brain (A), and coronal sections (B), with a brain weight of 880 g. Note the prominent temporal horn dilation with significant medial temporal atrophy in panel B. Panels C and D: Low power (C; original magnification 32X) and high power (D; original magnification 160X) photomicrographs of Bielschowsky stains in neocortex reveal frequent neuritic plaques and neurofibrillary tangles. Panel E: High power photomicrograph (original magnification 400X) of a Bielschowsky stain in hippocampus reveals numerous neurofibrillary tangles. Panels F, G, H: Immunohistochemical stains with diaminobenzidine (brown) chromogen for phosphorylated tau reveal strong, band-like immunoreactivity in all gray matter regions assessed. Panel F is low power (original magnification 16X) of hippocampus, showing the band of immunoreactivity in Sommer's sector. Panel G is high power (original magnification 160X) of neocortex revealing pretangles in neuronal perikarya as well as dense, diffuse neuritic staining. Panel H reveals a thorn-shaped white matter astrocyte, characteristic of ARTAG (original magnification 160X). Panel I displays an

immunohistochemical stain for β -amyloid in cerebellar folium, demonstrating an amyloid plaque at the granular cell-molecular layer interface (original magnification 160X).

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Figure 2.

Moderate Alzheimer's disease neuropathological changes in a functionally intact 81-year-old woman with long-term viral suppression (subject B). Panels A and B: Mild atrophy, seen in frontal regions on lateral view of the hemi-sectioned brain (A), and minimally in parietal regions on coronal sections (B), with a brain weight of 1050 g. Panels C and D: High power photomicrographs of Bielschowsky stains in neocortex (panel C, original magnification 160X) and hippocampus (panel D, original magnification 320X) reveal moderate numbers of neuritic plaques in neocortex; neurofibrillary tangles (one pictured in high power in panel D) were most prominent in mesial temporal lobe. Panels E and F display immunohistochemical stains for phosphorylated tau in neurons and neurites of temporal cortex (panel E, original magnification 400X), and astrocytes typical of ARTAG in temporal white matter (panel F, original magnification 400X). Panel G shows hematoxylin and eosin-stained section of frontal cortex with hyalinized arteriole classic for congophilic angiopathy. An arrow points

to an amyloid core, component of a neuritic plaque, in adjacent parenchyma (original magnification 320X). Panel H demonstrates an immunohistochemical stain for β -amyloid, confirming its presence in cerebral arterioles in congophilic angiopathy (original magnification 400X).

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