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Absence of PIttsburgh Compound B Detection of CerebralAmyloid Beta in a Patient With Clinical, Cognitive, and Cerebrospinal FluidMarkers of Alzheimer Disease

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Abstract

Objective—To determine the temporal relationships of clinical, cognitive, Pittsburgh Compound-B (PiB) amyloid imaging, and cerebrospinal fluid (CSF) markers of Alzheimer's disease (AD).

Design—A case report of a longitudinally assessed participant in a memory and aging study who had serial clinical and psychometric assessments over 6 years, in addition to PiB imaging and CSF biomarker assays, prior to coming to autopsy.

Setting—Alzheimer's Disease Research Center

Findings—An 85-year old individual was cognitively normal at his initial and next 3 annual assessments. Decline in measures of episodic memory and, to a lesser degree, working memory began

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at about age 88 years. PiB-PET amyloid imaging was negative at age 88.5 years, but at age 89.5 years there was reduced amyloid-beta 42 ($A\beta_{42}$) and elevated levels of tau in the CSF. At his 6th assessment, when he was 90 years old, he was diagnosed with very mild dementia of the Alzheimer type. After death at age 91 years, the autopsy revealed foci of frequent neocortical diffuse Aβ plaques, sufficient to fulfill Khachaturian neuropathologic criteria for AD, but neuritic plaques and neurofibrillary tangles were sparse. Postmortem biochemical analysis of the cerebral tissue confirmed that PiB-PET-binding was below the level needed for *in vivo* detection.

Conclusion—Clinical, cognitive, and CSF markers consistent with AD may precede detection of cerebral Aβ with amyloid imaging agents such as PiB, which primarily label fibrillar Aβ plaques.

The identification of sensitive and specific biomarkers of Alzheimer disease (AD) may improve its early diagnosis and may help to evaluate the efficacy of potential therapeutic interventions. [1–4] In particular, cerebrospinal fluid (CSF) assays of amyloid-beta-42 ($A\beta_{42}$) and tau and amyloid imaging tracers such as Pittsburgh Compound-B (PiB) [5] may identify the AD pathological process in the brain, regardless of clinical status (ie, whether or not cognitive impairment or dementia is present). [6–12] To our knowledge, there have been no reports of individuals who have been characterized longitudinally with clinical and cognitive measures and who transitioned from cognitive normality to early symptomatic AD during a period when both CSF markers and PiB amyloid imaging were obtained. We now report such a case, with clinicopathological evidence for AD, to provisionally examine the sequence of biomarker and neuropathological abnormalities in AD.

METHODS

PARTICIPANT

The case reported here comes from a sample of community-dwelling volunteers enrolled in a longitudinal study of healthy aging and AD conducted by the Washington University Alzheimer Disease Research Center. Participants in this longitudinal study are 60 years of age or older, in good general health, and have no neurological (other than AD), psychiatric, or systemic medical illness that could contribute importantly to dementia. They also have no medical contraindication to lumbar puncture (LP) or structural or functional neuroimaging. All procedures have been approved by the University's human subjects committee, and written informed consent is obtained from the participants and their collateral sources.

ASSESSMENTS

At entry and annual followup, experienced clinicians determine the cognitive status of participants based soley on semistructured interviews with the individual and their observant collateral sources (typically the spouse or adult child), followed by a neurological examination of the participant. Impaired cognition is detected when there is decline from previously attained cognitive abilities that interfere to at least some degree with the individual's performance in everyday activities. [13] The clinical battery includes the administration of the MiniMental State Examination (MMSE). [14] Based on all information, the clinician determines the Clinical Dementia Rating (CDR,) [15] where 0 indicates no dementia and excludes even minimal cognitive impairment, whereas CDR 0.5 indicates very mild dementia. In demented individuals, a diagnosis of AD is made in accordance with standard definitions and criteria. [16]

The CDR and dementia diagnosis is completed without reference to psychometric performance, which is obtained 2 weeks after the clinical assessment. The 1.5 hour psychometric test battery is administered annually. The tests include three measures of episodic memory: Logical Memory and Associate Learning from the Wechsler Memory Scale [17] and the Free and Selective Reminding Test (sum of three free recall trials). [18] There were two measures of semantic memory, Information[19] and the Boston Naming Test.[20] Working

memory measures included Mental Control and Digit Span (forward and backward) [17] and word fluency for S and P. [21] Visuospatial ability was assessed with Block Design [19] and Digit Symbol [19]and the Trailmaking Test A. [22] Scores can be converted to *z* scores using means and standard deviations from the first time of assessment of a reference group of 310 individuals who were enrolled as CDR 0 and remained that way as long as followed (for at least two assessments). [23]

At entry, a blood sample is obtained for determination of apolipoprotein E (*APOE*) genotype as previously described. [24]

CSF COLLECTION, PROCESSING, AND ASSESSMENT

Cerebrospinal fluid (20–30 mL) is collected at 8 AM after overnight fasting. Samples are gently inverted to avoid possible gradient effects, briefly centrifuged at low speed, and aliquoted into polypropylene tubes prior to freezing at −84°C. The samples are analyzed for total tau, phosphorylated tau_{181} ($ptau_{181}$), and $A\beta_{42}$ by enzyme-linked immunosorbant assay (Innotest; Innogenetics, Ghent, Belgium) as previously described. [7]

IN VIVO AMYLOID IMAGING

Positron emission tomography (PET) with PiB is obtained as previously described. [10] A "positive" PET-PiB image, denoting the presence of cerebral Aβ deposits, is defined by a mean cortical binding potential (MCBP) for PiB of 0.2 or more (averaging the binding potentials in prefrontal cortex, precuneus, lateral temporal cortex, and gyrus rectus). [10]

NEUROPATHOLOGICAL ASSESSMENT

Formalin-fixed tissue from fifteen standard cortical and subcortical regions are embedded in paraffin wax and sections cut at 7 μm as previously described.[25] Hematoxylin and eosin (H&E) and a modified Bielschowsky silver impregnation is used on representative brain areas. Immunohistochemistry is performed using anti-ubiquitin (1:1,000, rabbit polyclonal antibody (PAB; Dako, Glostrup, Denmark), anti-TDP-43 (1:4,000, rabbit PAB, ProteinTech Inc., Chicago, IL) anti-tau (PHF-1; a gift from Dr P Davies, Albert Einstein School of Medicine, NY, NY), anti-α-synuclein (1:500, mouse monoclonal antibody (MAB) LB-509; Zymed, San Francisco, CA), and anti-Aβ (1:100,000, mouse MAB, 10D5; gift of Eli Lilley, Indianapolis, IN) antibodies. Additional immunohistochemical and histological analyses utilize the 6E10 antibody, targeting amino acids 1-16 (N-terminus) of Aβ (1:3,000, mouse MAB, Signet, Emeryville, CA) and β-sheet markers 6-CN-PiB and X-34 (the highly fluorescent derivatives of PiB[26] and Congo red,[27] respectively.

NOTE: The neuropathologist is aware of the clinical diagnoses of autopsied participants. However, the clinical, psychometric, CSF, and PET-PiB imaging assessments are completed by investigators who are unaware of the results from the other assessments.

CASE REPORT

An 85-year-old male civil servant with 12 years of education and without a family history of dementia was CDR 0 (cognitively normal) at entry (T-1) and at the next 3 annual assessments through age 89 years (Figure 1). At age 90 years, his collateral source reported declining cognitive abilities with forgetfulness, poor decisional capacity, and mild interference with daily function (e.g., impaired driving abilities causing a motor vehicle accident). The participant could not recall reliably recent events in which he had participated. The MMSE score at age 90 was 26. He was diagnosed with very mild (CDR 0.5) dementia of the Alzheimer type (DAT) and died of congestive heart failure 6 months later, shortly after his 91st birthday. His *APOE* genotype was homozygous for ε3.

The longitudinal performance of this participant on measures of episodic memory, semantic memory, working memory, and visuospatial ability is shown in Figure 1. The most striking feature of Figure 1 is the two standard deviation drop on the episodic memory composite accompanied by a less precipitous decline in working memory (half a standard deviation), with maintained semantic memory and visuospatial ability.

At age 88.5 years a PET-PiB scan was unremarkable (PiB mean cortical binding potential = −0.006). At age 89.5 years CSF assays showed elevated total tau = 575 pg/mL (>500 pg/mL is abnormal) and $ptau_{181}$ = 83 pg/mL (>80 pg/mL is abnormal) and lowered $A\beta_{42}$ = 303 pg/mL (<500 pg/mL is abnormal), and $A\beta_{40}$ = 12,943 pg/mL, which was in the normal range.[7, 28]

The autopsy was performed 2.5 years after the PiB-PET scan. The unfixed brain weighed 1,310 g (normal range: 1,250 – 1,400 g). External examination showed no cerebral atrophy. Coronal slicing revealed mild to moderate dilatation of the lateral ventricle with rounding of the angle and only modest increase in space in the inferior horn; the hippocampus appeared only slightly smaller than normal. The substantia nigra and locus coeruleus were well-pigmented.

Microscopy of H&E stained tissue sections revealed some neuronal loss and gliosis throughout the frontal neocortex (not shown). There were sparse to focally numerous Aβ plaques (Figure 2) but only infrequent neuritic plaques. Isolated neurofibrillary tangles were seen using Bielschowsky silver staining and PHF-1 (not shown). There was no α-synucleinopathy and no TDP-43 proteinopathy[c1]. There was mild amyloid angiopathy and modest arteriolosclerosis. Moderate neuronal loss and gliosis in the CA1 subfield of the hippocampus were accompanied by modest granulovacuolar degeneration and several neurofibrillary tangles. There was also neuronal loss, gliosis, and a few neurofibrillary tangles, but no neuritic plaques, in the parahippocampal gyrus.

The AD lesions met neurofibrillary stage III for tangles and amyloid stage C for plaques in the Braak and Braak staging system. [29, 30] The densities of diffuse plaques were sufficient to meet the age-adjusted neuropathological criteria for AD according to Khachaturian, [31] but the low densities of neuritic plaques and tangles were consistent only with “possible AD” according to the Consortium to Establish a Registry for Alzheimer’s Disease [32] criteria, and there was only a “low” probability that the very mild dementia was caused by AD according to the National Institute on Aging-Reagan Institute (NIA-Reagan) criteria. [33] There was no evidence of any other neurodegenerative or clinically meaningful vascular disease.

Biochemical analysis of frozen brain tissue included [^{3}H]-PiB binding to brain tissue homogenates (Table 1). The binding levels were below those needed for *in vivo* PiB detection of fibrillar Aβ plaques, and X-34 and 6-CN-PiB histofluorescence staining revealed only scarce fibrillar Aβ plaques (Figure 3). [26, 27]

COMMENT

This case met conventional criteria for mild cognitive impairment (MCI).[34] Our clinicians, however, are trained to use the observations of a collateral source to detect an individual’s impaired ability to conduct accustomed activities (e.g., driving a motor vehicle) due to decline in that individual’s previously attained cognitive function. The clinician determines the CDR based on these observations and the clinician’s assessment of the individual, but without knowledge of the individual’s psychometric performance or imaging or CSF results. When an individual is determined to have cognitive impairment, even at the CDR 0.5 level, the clinician then judges the likely cause or causes of that impairment. If that cause is judged on clinical grounds to be AD, the individual is diagnosed with DAT. Although this diagnosis may occur at an earlier stage of symptomatic AD than is common elsewhere, and even at a stage where

psychometric performance is insufficiently impaired to meet criteria for MCI, it is supported by subsequent progressive cognitive and functional decline and by the histopathologic confirmation of AD in 92% of those individuals who come to autopsy.[13, 35]

The clinical diagnosis of very mild DAT (CDR 0.5) in this case was independently supported by cognitive decline in measures of episodic and working memory and by a CSF biomarker phenotype for AD, namely elevated tau and $ptau_{181}$ levels and reduced $A\beta_{42}$ levels. Neuropathological examination showed increased densities of diffuse plaques but more mature neuritic plaques were scarce and thus not likely to be identified *in vivo* by PiB-PET amyloid imaging.. These findings suggest that substantial densities of diffuse plaques, which themselves may be downstream of more toxic species of Aβ,[36] are not benign as they can be associated with very early symptomatic stages of AD. Hence, neuropathological criteria such as the NIA-Reagan recommendations[32] that do not incorporate diffuse Aβ plaques into their algorithms may overlook an important early pathogenic feature of AD.

Amyloid tracers such as PiB bind strongly to fibrillar Aβ in compact/cored plaques and cerebral amyloid angiopathy but only weakly to amorphous cortical Aβ plaques. [26, 37] These tracers thus may be unable to detect AD variants that are characterized predominantly by diffuse Aβ plaques. We reported previously that elevated mean cortical binding potential for PiB is almost always associated with low CSF $A\beta_{42}$ but that low levels of CSF $A\beta_{42}$ can occur in the absence of elevated mean cortical binding potentials for PiB, [6, 8] possibly because diffuse plaques can first appear in the absence of significant amount of fibrillar Aβ, as suggested by the current case. For individuals with substantial amounts of diffuse non-fibrillar Aβ deposits, reduced levels of CSF $A\beta_{42}$ may reflect AD pathology prior to the presence of sufficient fibrillar plaques to allow detection by PiB. Although this is but one case, it implies that a CSF profile of reduced $A\beta_{42}$ and elevated tau in nondemented individuals can serve as an antecedent biomarker for AD as it may predict future DAT.

A limitation of this single case study is the temporal dissociation between the various assessments. The scarcity of fibrillar Aβ plaques at autopsy, however, suggests that it is unlikely that the PiB-PET would have been positive even if imaging occurred closer to the time of lumbar puncture (one year later) or time of death (2.5 years later). Another limitation is that the battery of psychometric tests was chosen many years ago for the longitudinal study in which this man participated; it did not include the more sensitive measures of working memory that are available today. Newer instruments may have detected earlier and more profound decline in this domain. The battery also did not include measures of attention, which may also be affected very early in the course of the disease. [38]

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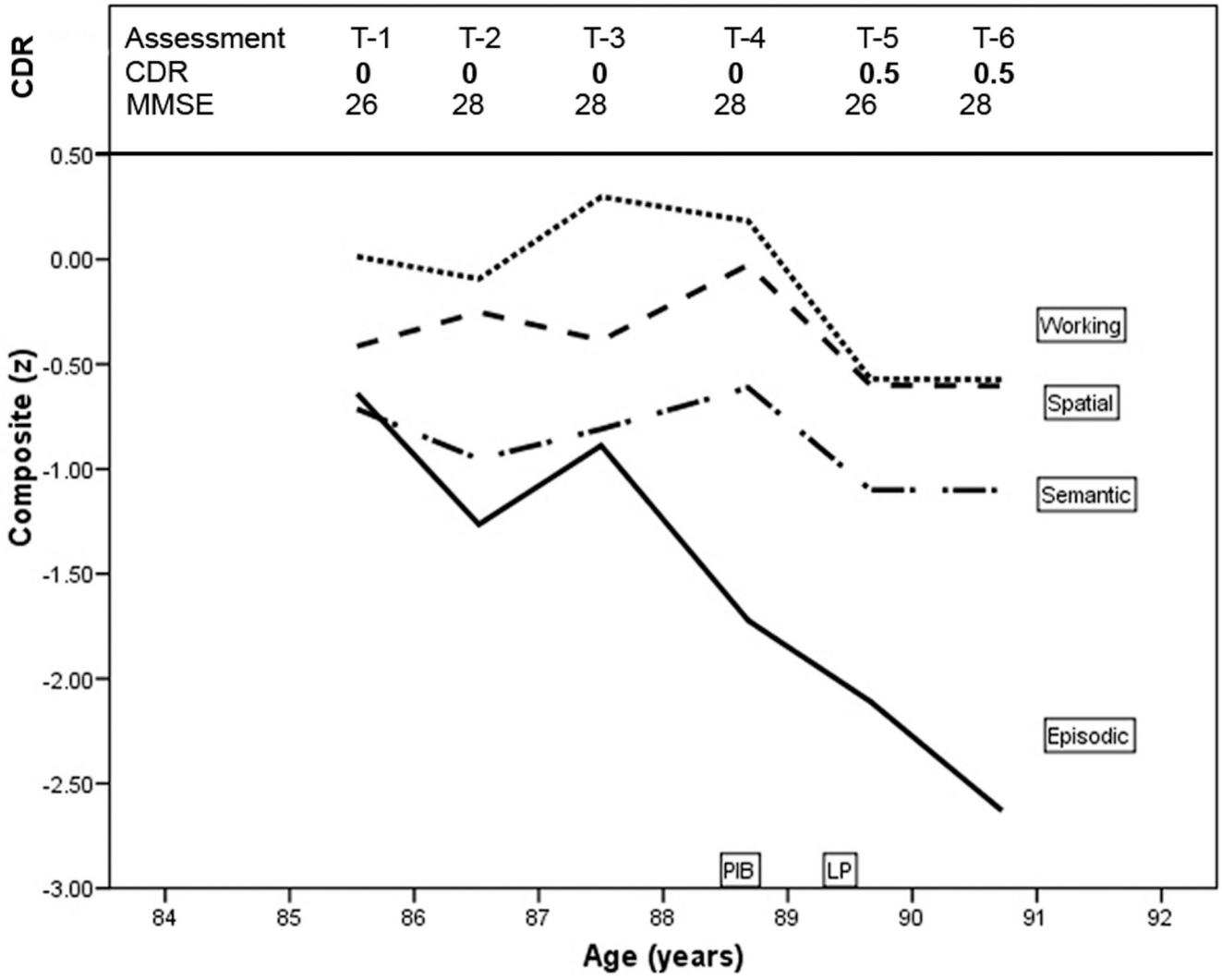

Figure 1.
Clinical and cognitive course of PiB-PET-negative case. T-1, first clinical assessment; CDR, Clinical Dementia Rating; z score, the means of four neuropsychological test composites: episodic memory, semantic memory, working memory, and visuospatial ability.

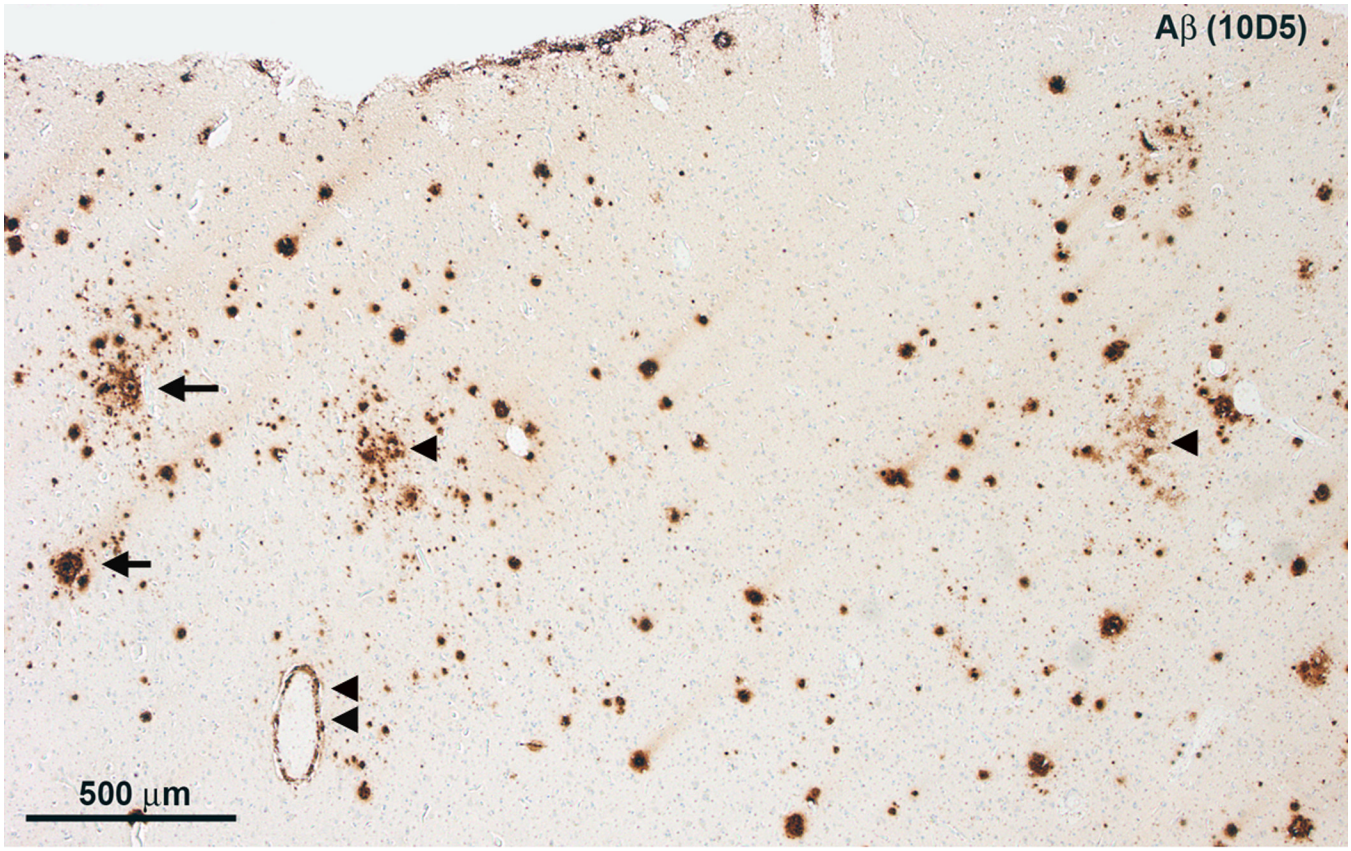

Figure 2.
Microscopy of the left frontal lobe. A, There are numerous diffuse Aβ plaques (arrowheads), but only few ring-with-core plaques (arrows) and modest cerebral amyloid angiopathy (double arrowhead).

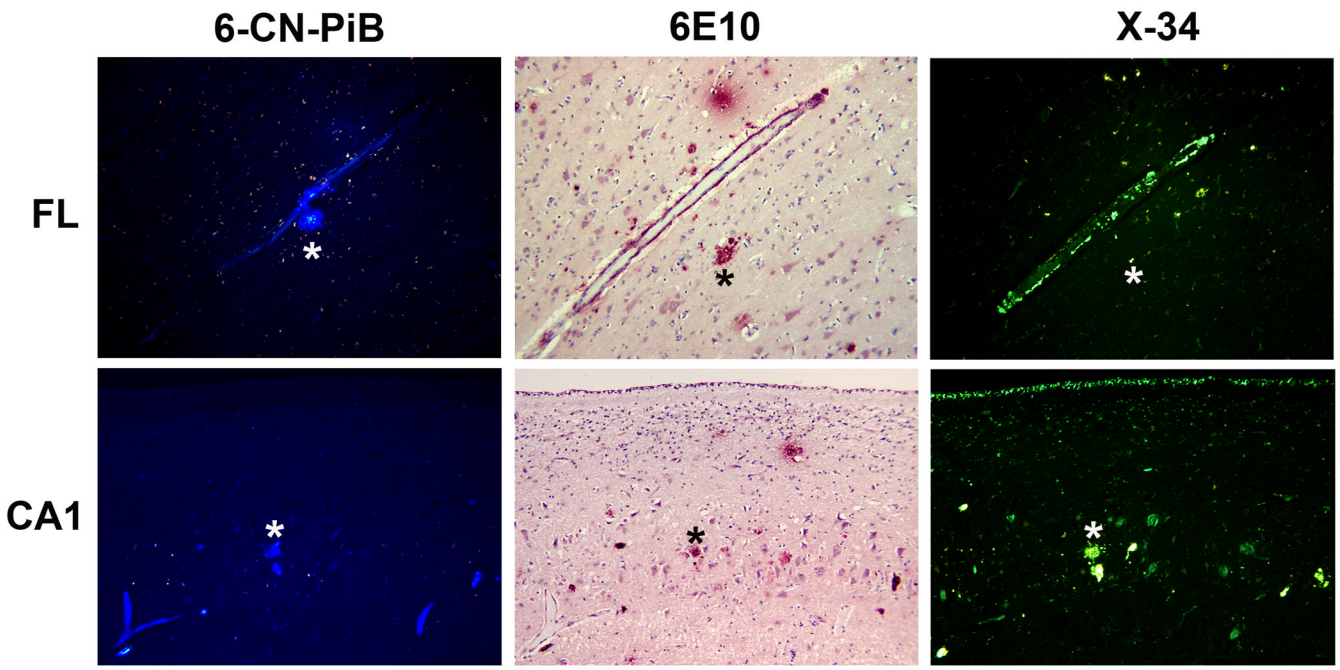

Figure 3.

Fluorescent β-pleated sheet stains label a spectrum of Aβ structures in the frontal lobe (upper panels) and CA1 subfield of hippocampus (lower panels) of postmortem brain of PiBPET-amyloid-negative participant. Amyloid is visible using 6-CN-PiB and X-34, highly fluorescent derivatives of PiB[17] and Congo red[18], respectively; the monoclonal antibody 6E10, targeting amino acids 1-16 (N-terminus) of Aβ identifies similar structures as denoted by the asterixes.

Table 1

PiB cortical binding potential in PiB-negative participant and Aβ load at autopsy

Aβ	FL	AC	TL	PL	PC	OL	Mean
PiB Mean BP	−0.04	−0.33	0.07	0.43	0.15	0.01	0.05*
Aβ load (area fraction of 10D5 (%))	4.4	1.6	2.0	2.9	5.4	0.9	2.9
Aβ load [3H]PiB bound(pmol/g)	249	124	161	116	225	295	195
Aβ load ($Aβ_{42}$pmol/g)	1582	837	722	687	1785	1525	1190

Abbreviations: FL, superior frontal gyrus of frontal lobe; TL, superior temporal gyrus; PL, inferior parietal lobe; OL, calcarine sulcus of occipital lobe; AC, anterior cingulate gyrus; PiB BP = binding potential as calculated by the Distribution Volume ratio minus 1.0;

* indicates that cortical BP is less than that of white matter (0.34).