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Isolated Executive Impairment and Associated Frontal Neuropathology

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Key Words
Isolated executive impairment · Cortical neurofibrillary tangles · Amyloid peptides · Cingulate gyrus · Mild cognitive impairment

Abstract
Cognitive impairment in the absence of dementia is common in elderly individuals and is most often studied in the context of an isolated impairment in memory. In the current study, we report the neuropsychological and neuropathological features of a nondemented elderly individual with isolated impairment on a test of executive function (i.e., Trail Making Test) and preserved memory, language, and visuospatial function. Postmortem studies indicated that cortical neurofibrillary tangles (NFT) varied considerably, and some regions contained large numbers of neuritic senile plaques. Semiquantitative immunohistochemistry showed higher NFT and amyloid-beta (Aβ) loads in the frontal cortex relative to the temporal, entorhinal, occipital, and parietal cortices. A survey of the entire cingulate gyrus showed a wide dispersion of Aβ42 with the highest concentration in the perigenual part of the anterior cingulate cortex; Aβ appeared to be linked with neuron loss and did not overlap with the heaviest neuritic degeneration. The current case may represent a nonmemory presentation of mild cognitive impairment (executive mild cognitive impairment) that is associated with frontal and anterior cingulate pathology and may be an early stage of the frontal variant of Alzheimer disease.

Introduction

Cognitive impairment in the absence of dementia in individuals over age 65 is 2–5 times more common than dementia [1]. To date, isolated memory impairment has been the primary focus of these studies. The term 'mild cognitive impairment' (MCI) is commonly used to categorize nondemented elderly who exhibit isolated memory impairment and a relative preservation of other cognitive domains and activities of daily living [2]. Individuals with MCI are at an increased risk for Alzheimer disease (AD) [3]. Despite the focus on memory impairment, the clinical outcome of isolated impairment in other cognitive domains such as executive function is not known. The current study describes a nondemented elderly subject with isolated executive impairment and preserved memory function.

Methods

We evaluated a 68-year-old female with 16 years of education as part of a longitudinal study of healthy elderly. She completed one neuropsychological evaluation (table 1). No brain MRI was performed. Her medical history included tonsillectomy, coronary artery disease, hypertension, and hypercholesterolemia. Her social history included occasional alcohol use, and she had smoked 1/3 pack of cigarettes per day for 20 years. The subject died 20 months after the evaluation following an acute myocardial infarction.

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Table 1. Neuropsychological test results

MMSE	29/30
Memory	
CERAD Word List Learning Task	
Trial 1	7/10
Trial 2	8/10
Trial 3	8/10
5-min delayed recall	8/10
5-min recognition	20/10
30-min delayed recall	8/10
30-min recognition	20/10
WMS-R Visual Reproductions	
Immediate recall	40/45 (99th percentile)
30-min delayed recall	25/45 (67th percentile)
Language	
Boston Naming Test – modified	29/30
CERAD Animal Naming	18
Abstract reasoning	
WAIS-R similarities	24 (scaled score 12)
Visuospatial	
CERAD constructional praxis	10/11
WAIS-R block design	24 (scaled score 11)
Executive	
TMT-A	79 (MOANS scaled score 3)
TMT-B	123 (MOANS scaled score 7)

MMSE = Mini-Mental State Exam; CERAD = Consortium to Establish a Registry for Alzheimer Disease; WMS-R = Wechsler Memory Scale – Revised; WAIS-R = Wechsler Adult Intelligence Scale – Revised; MOANS = Mayo's Older Americans Normative Studies.

Tissue Preparation and Diagnosis

The postmortem interval was 8.5 h and the brain was removed and postfixed in 10% formalin. A standard neuropathological examination (R.K.) was performed for diagnostic purposes [4]. Blocks from Brodmann's areas (BA) in the frontal cortex (BA6, 8, 9, 10, 11), entorhinal cortex (BA28), inferior parietal cortex (BA7), temporal cortex (BA22), and occipital cortex (BA17) were sectioned at 50 μm using a vibratome. The left cingulate gyrus and adjacent cortex were removed following brain cutting into 1-cm slabs and the medial surface was reconstructed and photographed (fig. 2). The blocks were cryoprotected in graded sucrose and cut into 8 series of 50-μm-thick sections on a cryostat.

Immunocytochemistry

Antibodies to β-amyloid (Aβ1–17; 6E10, 1:5,000; Signet Laboratories) were used to label senile plaques (SP). Mature neurofibrillary tangles (NFT) were evaluated with PHF-1 (1:1,000, provided by Peter Davies, Albert Einstein College of Medicine), and early NFT were analyzed with AT8 (1:10,000; Pierce Biotechnology). Sections immunostained for Aβ were pretreated with 90% formic acid for 4 min. Cingulate cortex sections were reacted with Aβ1–42 and 1–40 antibodies (Oncogene Research) and AT8 (Innogenetics), and a separate series of sections was stained with thionine.

Image Analysis

Ten individual 525-by-410-μm fields in 5 superficial cortical layers and 5 deep cortical layers adjacent to white matter were digitized for each brain region. The proportion of area occupied by Aβ and NFT immunostaining was quantified using gray-scale thresholding with NIH Image 1.55 [5]. The left cingulate gyrus was qualitatively analyzed with sections from each of 7 1-cm-thick blocks. Relative differences in Aβ40, Aβ42, AT8, and neuron densities were evaluated with a systematic photographic series and relative differences in each marker related to a comprehensive cytoarchitecture map [6].

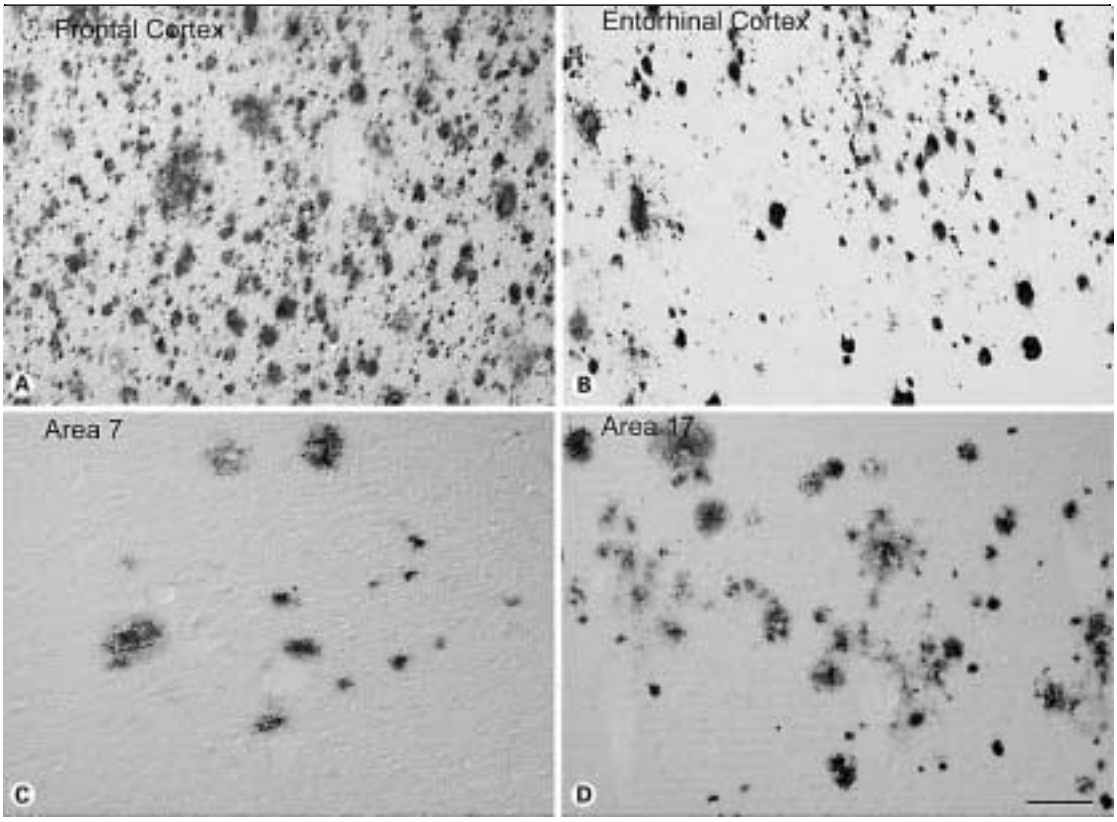
Results

Neuropsychological Testing

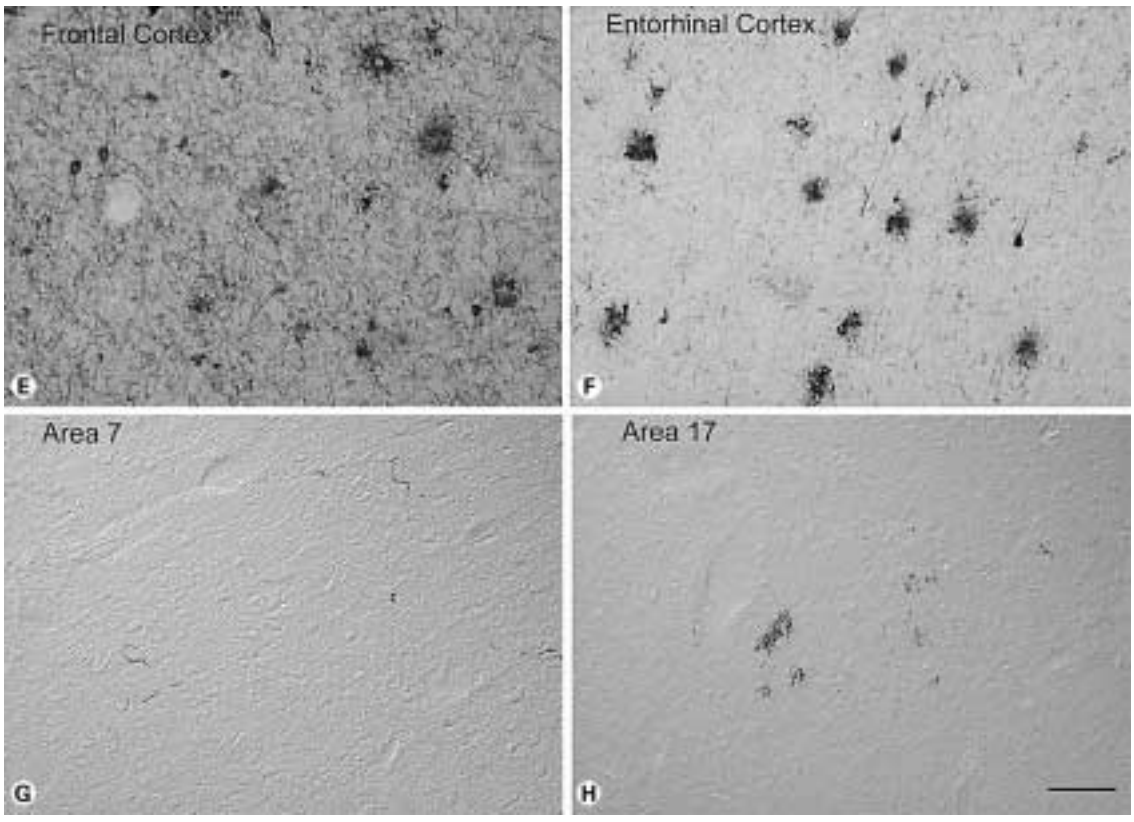
The subject scored 29/30 on the Mini-Mental State Examination. There was no evidence of depression on the Geriatric Depression Scale [7]. She performed within the normal range on all tests of memory, language, and visuospatial skills (table 1). However, her score on the Trail Making Test (TMT)-A fell in the severe impairment range, and her score on TMT-B fell at the borderline. The TMT [8] is a visuomotor scanning task that presumably involves the frontal cortex [9]. The family declined a postmortem interview. However, medical records were reviewed, and there were no complaints about cognitive difficulties, and the subject continued to drive and maintain typical activities, suggesting that she was not demented.

Neuropathological Findings

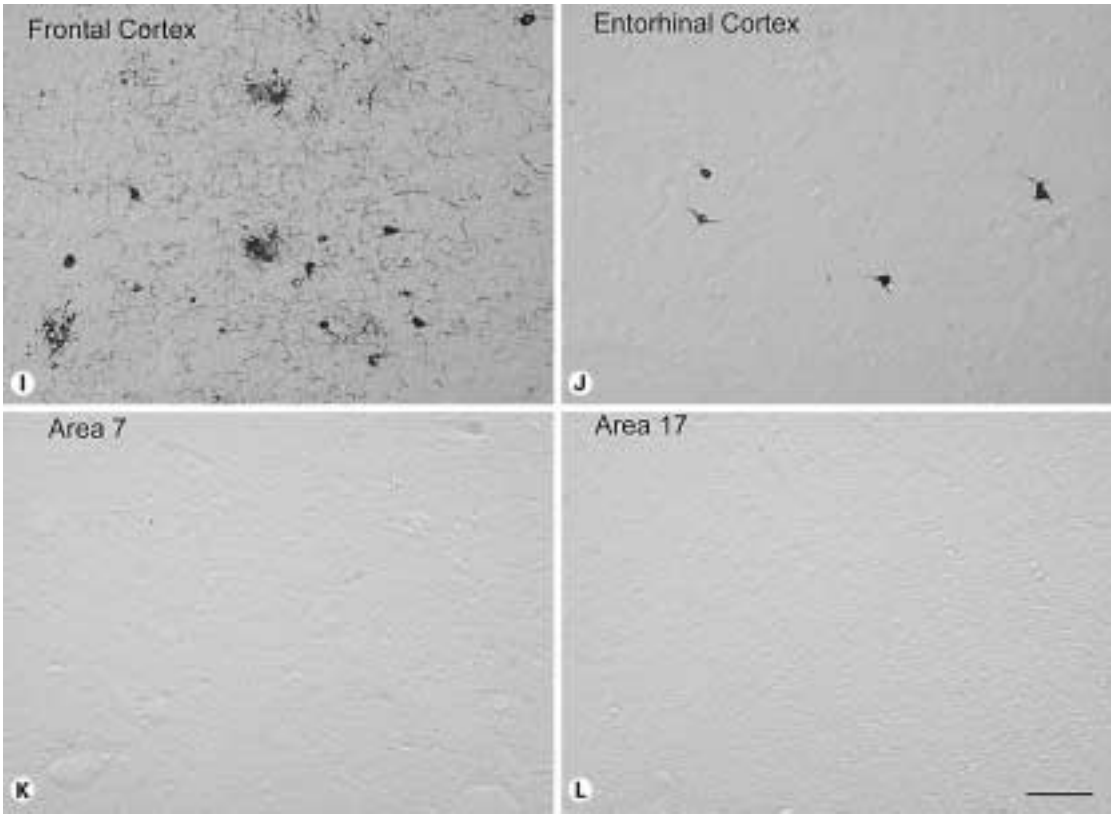
The brain weighed 1,250 g and appeared normal with no evidence of atrophy or ventricular enlargement. SP were widespread with extensive neuritic plaques in some cortical regions. The pre-α and pri-α layers of the entorhinal cortex (BA28) contained moderate to heavy NFT. Although the subiculum contained moderate NFT, area CA1 of the hippocampus was relatively mild. In all of the neocortical regions, NFT were infrequent but the amygdala contained a moderate number. Within the Sommer's sector and subiculum, granulovacuolar degeneration was readily observable. NFT and SP accumulation were of insufficient numbers to meet neuropathological criteria for AD [4]. There was no evidence of Pick bodies, Lewy bodies, infarcts, extensive white matter gliosis, glial tangles, or superficial vacuolation that is common in frontotemporal lobar degeneration (FTLD).


Frontal Cortex
Entorhinal Cortex
A
B
Area 7
Area 17
C
D

A–D


Frontal Cortex
Entorhinal Cortex
E
F
Area 7
Area 17
G
H

E–H



I–L

Fig. 1. A–D 6E10 (Aβ1–17) immunolabeling of SP in the frontal and entorhinal cortex, and areas 7 and 17. Aβ was characterized as diffuse deposits and was most extensive in the frontal cortex. **E–H** A similar pattern of AT8 (early NFT) immunoreactivity but with the majority of AT8 within clusters of dystrophic neurites. **I–L** Mature tangle formation visualized using anti-PHF-1 antibody. Bar = 100 μm.

Table 2. SP and NFT loads in individual cortical regions

Marker	Antibody	Area 8	Area 9	Area 6	Area 10	Area 11	Area 28	Area 7	Area 17	Area 22
SP	6E10	6.09	2.83	4.82	3.89	4.06	4.69	2.35	4.98	2.92
NFT	AT8	9.07	0.01	1.36	0.10	0.03	1.11	0.02	0.00	2.17
NFT	PHF-1	1.46	0.02	0.01	0.04	0.01	0.07	0.00	0.16	0.03

Quantification of SP and NFT

Table 2 shows that the highest level of Aβ, AT8 and PHF-1 was observed in BA8. NFT were sparse in the other brain regions except in BA22 and BA28. Figure 1 illustrates SP (fig. 1A–D), early NFT (fig. 1E–H) and mature NFT (fig. 1I–L) in 4 cortical areas. Note that the majority of the AT8 and PHF-1 was in clusters of dystrophic neurites with infrequent intracellular NFT. Thus, AT8 and PHF-1 loads reflect neuritic degeneration rather than intracellular NFT.

Cingulate Gyrus Pathology

Figure 2 is a reconstruction of the medial surface and samples of Aβ42 immunoreactivity from each of the 7 blocks through the cingulate gyrus. Sections 1–4 had heaviest deposition in areas 32 and 32′ and area 24c′ and

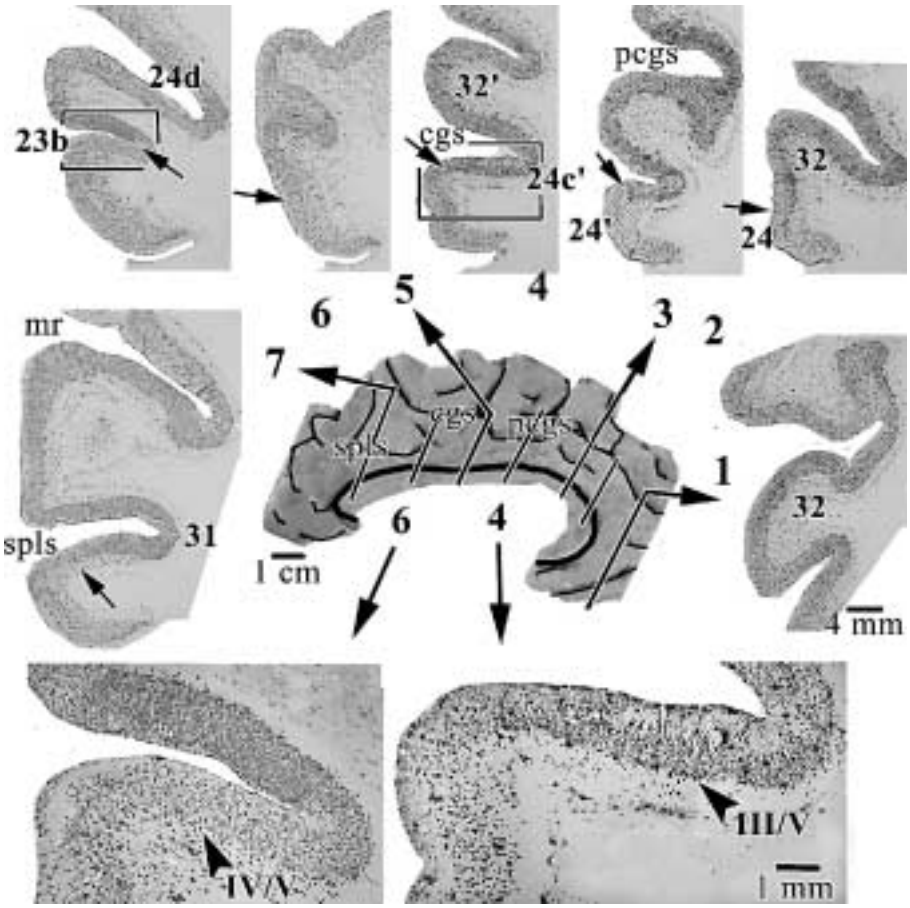


Fig. 2. Reconstruction of the medial surface with the following structures: cc = Corpus callosum; cgs = cingulate sulcus; pcgs = paracingulate sulcus; spls = suprasplenial sulci; mr = marginal ramus of the cgs. Aβ42-immunoreacted sections are shown from 7 levels in this and the next figure and each arrow in sections 2–7 marks an approximate border between qualitatively low or high amounts of Aβ42. Arabic numbers overlying each section are for cytoarchitectural areas. The boxes in sections 4 and 6 are of sections with high/low levels of Aβ42 magnified below where the arrowheads show the borders between layers III/V and IV/V, respectively.

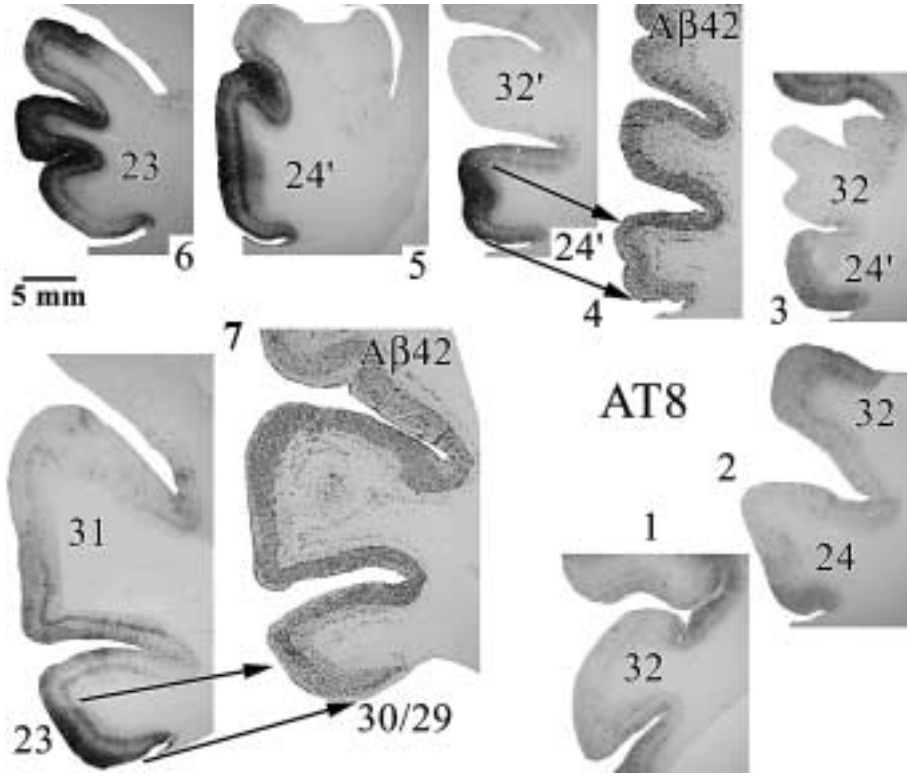


Fig. 3. Distribution of AT8 at the same levels as in figure 2 with direct comparisons for levels 4 and 7 to emphasize the nonoverlapping nature of AT8 with Aβ42, particularly within the pairs of arrows for area 24′ in level 4 and area 23 in level 7. Notice how striking AT8 is in posterior area 24′ and areas 23, 30, and 29 and the lack of overlap with high levels of Aβ42.

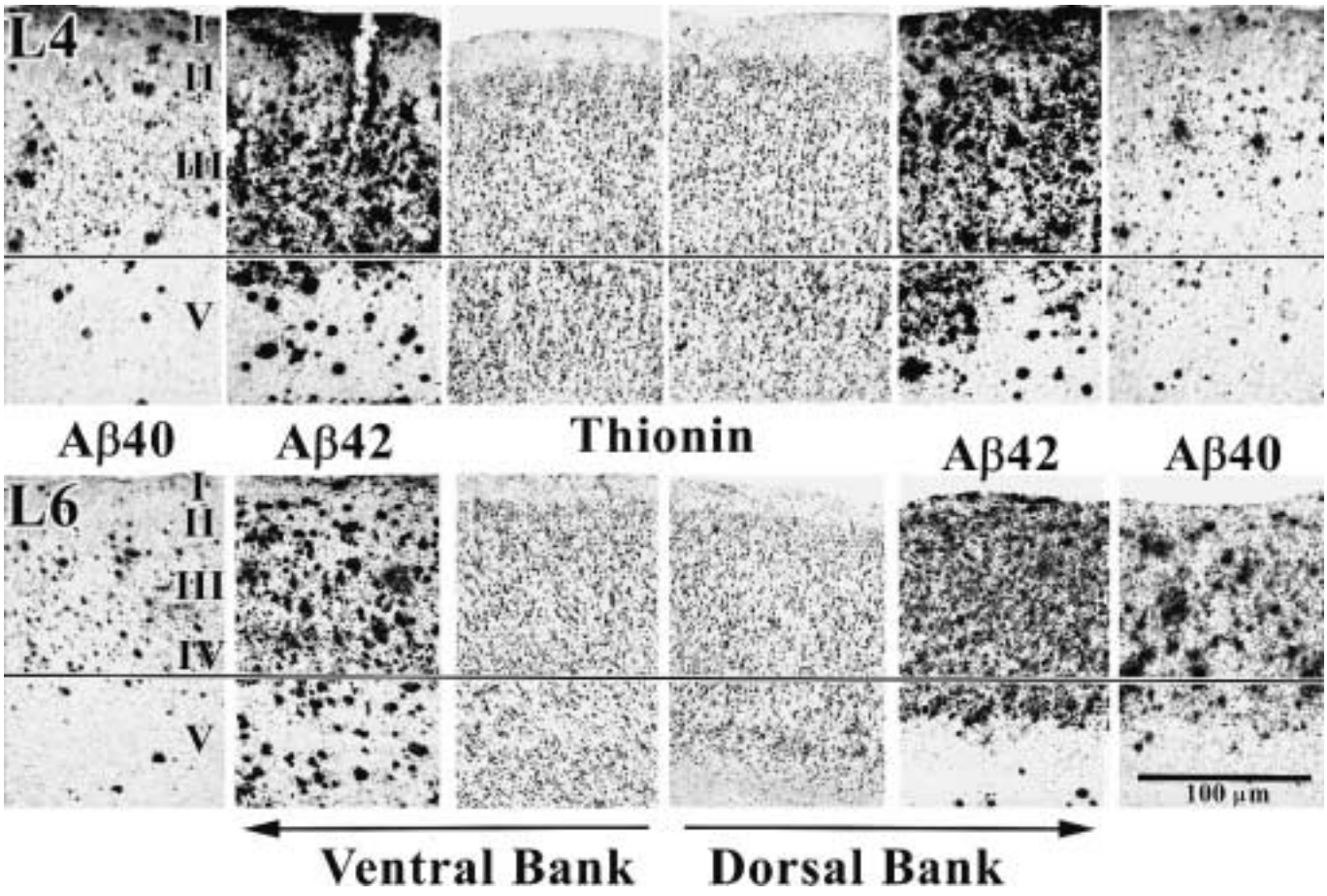


Fig. 4. Comparison of markers at levels 4 (L4) and 6 (L6) above and below the cingulate sulcus, for area 24d at L4 and for area 23b at L6 above and below the splenial sulci. Although Aβ40 does not appear to determine the extent of neuron loss, there is a high amount of Aβ42 in area 23b of the dorsal bank of the suprasplenial sulci where there is a paucity of neurons in layers II–IV (L6, thionine, above the line). There is a correlation with a high amount of Aβ42 in both upper and lower banks of area 24d showing a paucity of neurons throughout layer III (L4, above the line).

posterior areas 31 and 23b had heavy deposits in levels 5–7. AT8 immunoreactivity was greatest in caudal mid-cingulate and posterior cingulate cortices and did not overlap with the heaviest deposits of Aβ42. Areas 32, 32′, 31, and rostral area 24′ are strikingly free of AT8 (fig. 3). In contrast, caudal area 24′ and area 23 have very high levels. The lack of overlap of these markers is emphasized in figure 3 that directly compares Aβ42 in 2 levels to that in AT8 and shows their differential deposits. In level 4, the gyral surface shows a high amount of AT8 and a low to moderate amount of Aβ42, while in level 7, a high amount of AT8 in areas 23 and the sulcal retrosplenial areas 30 and 29 is associated with a low amount of Aβ42.

Neuron densities can be evaluated in levels 4 and 6 (fig. 4). Level 4 in the cingulate sulcus had a high amount of Aβ42 and a low amount of Aβ40 in layers I–III, little of both Aβs in layer V, and virtually no AT8. Neuron densities in the deep layers appear relatively normal (i.e., below the line separating layers III and V). In contrast, there is a thinning of neurons in layer III in both the dorsal and ventral banks of the cingulate sulcus.

Area 23b (level 6, fig. 4) in the dorsal bank of the splenial sulcus has a high Aβ42/40 level, and its ventral bank has a much lower amount, while the ventral bank has high AT8 and the dorsal bank low AT8 levels. Layer III is neuron sparse in the dorsal bank of the splenial sulcus, and the cortex appears thin when compared to the ventral bank.

Discussion

The current report describes an elderly individual with an isolated impairment on the TMT and normal performance on other cognitive tests. The impairment on the TMT was the only clinical indicator of underlying neuropathology. SP and NFT were in highest concentrations in the frontal cortex compared to other more ventral and posterior regions. A complete examination of the cingulate cortex also exhibited a range of Aβ42. Aβ accumulation was observed in the rostral and dorsal cingulate cortex, whereas AT8 immunostaining was greatest in the caudal midcingulate and posterior cingulate cortex and did not correlate with Aβ accumulation.

Isolated Executive Impairment: Normal or Pathological Aging?

While some decline in executive function is a part of normal aging [9], the presence of a pronounced impairment may signify pathological aging. In the current study, the subject exhibited a severe and isolated impairment on the TMT, but did not meet criteria for dementia. Therefore, this pattern may represent a nonmemory presentation of MCI (amnestic MCI vs. executive MCI) and is similar to other studies that found AD neuropathology in amnestic MCI [10]. However, the distribution of neuropathology in our case is different in that the most prominent accumulation of SP and dystrophic neurites associated with SP occurred in the frontal cortex. Intracellular NFT were infrequent in the frontal cortex, but clusters of SP-associated dystrophic neurites were observed. Thus, the current report supports the hypothesis that a nonmemory cognitive impairment can be associated with AD-like neuropathology and may represent an executive presentation of MCI.

Frontal and Cingulate Gyrus Pathology: Normal or Pathological Aging?

A wide range of AD neuropathology has been reported in studies of nondemented elderly individuals. In individuals under age 70, the frequency of NFT and SP in various brain regions can be low [11]. However, up to 60% of subjects between 60 and 69 years of age showed SP but no NFT in the frontal cortex [12]. The subject in the current study showed the hallmark pathologies of AD including NFT and SP that were present in higher levels than in nondemented individuals in the sixth decade [13] and is unlikely to represent 'normal' aging. Thus, the presence of neuritic SP in the frontal cortex of the current case may signal mild AD.

In the cingulate gyrus, similar atypical distributions of SP and NFT were observed and appeared independent. In AD, the distribution of NFT and SP overlap with each other as well as with laminar patterns of neurodegeneration [14]. In this case, however, SP and NFT/neuritic changes did not generally overlap, and SP were prominent in the anterior and dorsal cingulate cortex. The differential SP and NFT deposition in the cingulate gyrus suggests a link with the extensive Aβ accumulation in the frontal cortex and may indicate that AT8 is marking degenerating neurites that precede neuron loss.

Is Isolated Executive Impairment a Precursor for the Frontal Variant of AD?

The current case raises the possibility that isolated executive impairment may be a prodrome for AD, and possibly the frontal variant of AD. The frontal variant of AD is associated with a disproportionate impairment of executive function and a greater than expected degree of NFT in the frontal cortex [5, 15–18]. Isolated executive impairment may also be a precursor for FTLD or vascular dementia [3] and possibly frontal variant AD. Our case lacked neuropathological signs of FTLD or vascular dementia. The predominance of neuritic pathology and SP in the frontal cortex of the current case appears similar to a previous report of a frontal variant of AD [5]. In the frontal variant of AD, frontal NFT but not SP pathology differentiated the two groups. It is possible that with time, the current case may have developed dementia and intracellular cortical NFT. The greater-than-expected accumulation of pathology in frontal and anterior cingulate cortices supports the hypothesis that selective cognitive deficits may reflect early and focal neuropathology.

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