

Alzheimer's Disease or Plaque Disease? Two Cases at the Frontier of a Definition

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Abstract

Atypical dementias confront the adequacy of current diagnostic concepts. The two patients with atypical dementia syndromes described here shared common postmortem features of numerous neocortical neuritic (senile) plaques and microvascular amyloid, sparing of hippocampus and substantia nigra, and the virtual absence of neurofibrillary tangles. Microscopically, the two differed only by the presence of a few subcortical Lewy bodies in case 1. These similar morphologic features were associated with dramatically different clinical presentations. In the first patient, visual hallucinations, Capgras' syndrome, cognitive slowing, myoclonus, parkinsonism, and primitive reflexes evolved over 3 years. Memory and language were relatively spared. In the second, dysphagia, nonfluent aphasia, hypophonia, motor perseveration, and a severe disorder of attention developed during this 18-month illness. At autopsy, an unrecognized colon malignancy was found. Despite high neuritic plaque counts in cortex, neither the clinical nor the pathologic criteria for Alzheimer's disease adequately describe either case. The cases will be examined first as clinical, then as neuropathologic, entities. From this approach, we conclude that a specific clinical dementia syndrome may be expressed by several neuropathologic "diseases" and that a variety of clinical syndromes may represent a single neuropathologic diagnosis. This strategy identifies a conceptual dichotomy between Alzheimer's syndrome and postmortem Alzheimer's disease. Meticulous clinical and neuropathologic observation is essential in advancing an understanding of the relationship between the two. (*J Geriatr Psychiatry Neurol* 1992;5:200-209).

Alzheimer's disease (AD) might be viewed as a clinical dementia syndrome that becomes a "disease" when accompanied by specific neuropathologic features. Two consensus groups have established the most widely accepted clinical criteria for AD.^{1,2} Neuropathologic diagnostic criteria published by Khachaturian define an age-dependent density of neocortical senile and neuritic plaques (NP), with older patients requiring higher plaque counts to fulfill diagnostic criteria. Hippocampal neurofibrillary change, often considered to be a key feature of AD, is not discussed, and the presence of neocortical neurofibrillary tangles (NFT), a criterion

for patients under age 50 years, becomes "optional" in older age groups.^{3,4} This age qualification is unique to neuropathologic diagnosis.

Most patients with the AD syndrome have AD neuropathologic changes discovered at necropsy by traditional staining techniques, but some have the syndrome in the absence of characteristic AD neuropathology,⁴⁻⁶ and others have AD neuropathology in the absence of a dementia syndrome.^{7,8} This disparity is reiterated by patients with unusual dementia syndromes associated with some or all of the neuropathologic features of AD. Such cases challenge the adequacy of accepted clinical and neuropathologic criteria and pose more fundamental questions about the relationships between pathologic processes in the brain and their clinical expression.

Each of the two patients described here had an atypical dementia syndrome. In the first, visual hallucinations, Capgras' syndrome, and parkinsonism predominated. In the second, dysphagia and cough

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marked the beginning of an 18-month illness characterized by progressive aphasia and dementia with frontal features. Postmortem features common to both cases included high densities of neocortical and subcortical A4 amyloid-positive NP, microvascular amyloid, few NFT, and sparing of both hippocampus and substantia nigra.

To explore the links between neuropathology and illness, each case will be viewed first as a clinical disorder to be compared with other dementing conditions bearing similar features. The cases will then be examined as *neuropathologic* entities demonstrating substantial differences from usual AD neuropathology despite meeting AD diagnostic criteria. These differences may have important implications for the pathogenesis of AD.

Case 1

At age 73 years, this right-handed man, a former garment worker, first experienced several periods of disorientation. When hospitalized the following year with paroxysmal atrial fibrillation and urosepsis, he did not recognize family members and had visual hallucinations of circus animals. Limb myoclonus, masked facies, hypophonic speech, and cognitive impairment were observed. An electroencephalogram (EEG) showed diffuse slowing. Other studies including head computed tomographic (CT) scan, thyroid function tests, serum levels of vitamin B₁₂ and folate, syphilis serology, and electrolytes were negative or normal. A neurologic consultant attributed these symptoms to a toxic encephalopathy and possible Parkinson's disease.

The symptoms and signs cleared over 2 months, only to reappear gradually several months later. At that time, he had a dementia characterized by impaired abstraction, compromised constructions, mild involvement of memory, and relative sparing of language. He performed well on simple tests of attention and vigilance, was fully oriented, and recalled two of four words at 10 minutes. He had frequent hallucinations of insects, priests, and nuns, often in his peripheral visual fields, primarily in dim light. Occasional vertical diplopia occurred during which he saw one object above another. He acknowledged the peculiar and bland nature of these visual experiences.

Following 15 months of illness at age 74 years, he acquired the persistent delusion of having two identical wives, one being an impostor (Capgras' syndrome). Occasionally, he verbally attacked his "real" wife, mistaking her for the other. Concur-

rently, bradykinesia appeared, associated with a shuffling gait, difficulty turning, diminished arm swing, and falling to the left. A T₂-weighted head magnetic resonance imaging (MRI) study was normal, without atrophy or increased white-matter signal (Figure 1). At this time, the patient's younger sister, then 73 years old, presented to one of the authors (P.E.) with a typical Alzheimer's dementia syndrome. His two brothers remained well.

By age 75 years, the tempo of his illness accelerated, particularly during the final 6 months. Drooling, dysarthria, hypophonia, and increased muscle tone appeared associated with impaired upward gaze, a positive glabellar tap sign, and primitive reflexes. He slept poorly and fell frequently. Hallucinations of insects on his food and blood on his hands disrupted his meals. He could not manipulate silverware, use the toilet, or operate water taps. He was unable to read and reported "foggy" vision (despite a recent examination demonstrating visual acuity of 20/30). He misidentified family members, had difficulty with visual fixation, and often missed the mark when reaching for objects. Several episodes of unresponsiveness occurred, during which he appeared to be quietly awake. He reported one such spell to his physician a week after it occurred. Repeatedly he expressed anger, frustration, and despair with his disabling illness.

In the final weeks of life, he was distractible, restless, and out of touch with his environment and appeared to be hallucinating. He jerked violently when startled. Myoclonus was prominent in the right lip and forearm, accompanied by extensor finger clonus. Plantar responses remained flexor. Voluntary gaze was limited to rare horizontal saccades. The EEG showed diffuse slowing. Head CT was again negative, and routine cerebrospinal fluid studies were normal.

Phenytoin did not relieve his agitated, inattentive state, but he became calmer and more lucid following the introduction of thiothixene. Occasionally, he recognized his surroundings and family members in the days preceding his death from aspiration pneumonia at age 76 years.

Neuropathologic Findings

Autopsy was limited to the brain (weight unavailable), which was fixed in 10% formalin and phenol. The cerebral hemispheres were symmetrical, with mild sulcal widening and gyral narrowing in frontal and central regions. The ventricles were small. Cerebellum and brain stem appeared normal grossly and when sectioned at 5- to 10-mm intervals. The sub-

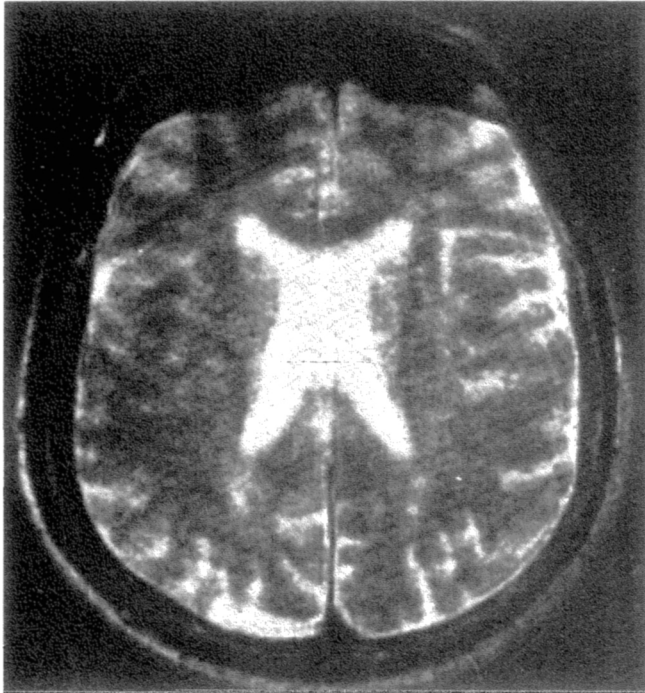


Figure 1A

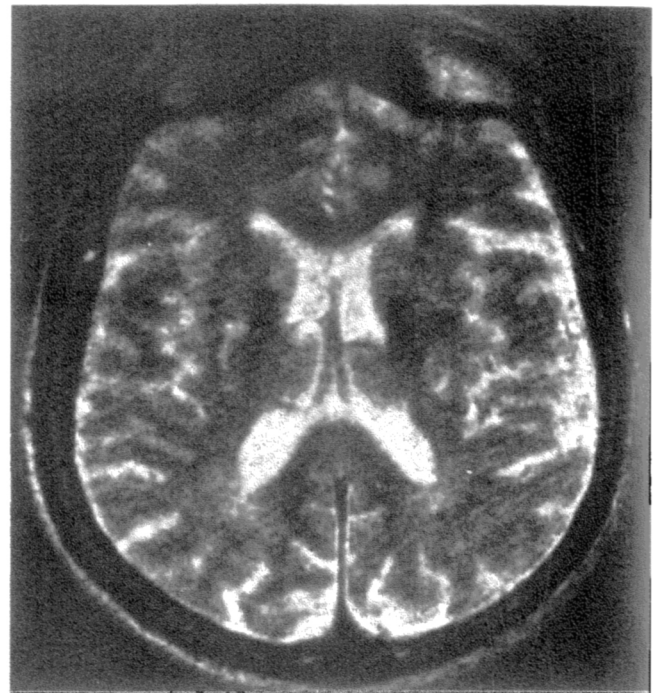


Figure 1B

FIGURE 1

Transverse T₂-weighted MRI scans show no abnormalities in case 1.

stantia nigra was adequately pigmented. Microscopic sections showed white-matter vacuolization due to phenol fixation. The white matter was otherwise free of gliosis or small-vessel disease. The cerebral cortex had preserved neurons, little or no astrocytosis, and no spongiform change. Bielschowsky silver stain preparations showed NP in excess of 15 per 200× high-power field in the cingulate gyrus and orbitofrontal and temporal cortex, with somewhat fewer in the occipital cortex and subiculum (range, 2 to 11), but no NFT. In cingulate, the absence of NFT was confirmed by negative immunostaining for NFT antigens with Ab 39 and Alz 50.⁹ Immunohistochemical studies of cortex and hippocampus for Alzheimer A4 peptide were performed as previously described.¹⁰⁻¹² In neocortex up to 25 A4-positive plaques were encountered per high-power field. Most NP were diffuse. The few with dense amyloid cores (Figure 2) were associated with dystrophic neurites that stained with silver and anti-ubiquitin but not Ab 39.¹³ A4-positive microvessels, including arterioles, were seen almost exclusively in the subarachnoid space.

In the hippocampus, anoxic eosinophilic shrunken neurons appeared in Sommer's sector, which was

otherwise well preserved. Granulovacuolar degeneration and NFT were rarely seen. A4 immunostaining of hippocampus showed small numbers of diffuse plaques, a rare plaque with a strongly positive A4 core, and no A4-immunoreactive microvessels.

Subcortical structures were well preserved, with small numbers of NP in caudate and putamen and larger numbers in thalamus, hypothalamus, and mammillary bodies by Bielschowsky stain. The substantia nigra showed mild loss of neurons and pigment. Ubiquitin immunostaining detected several Lewy bodies in substantia nigra, periaqueductal gray matter, the ventral tegmental region, and posterior hypothalamus. Rare ubiquitin-positive Lewy bodies (0 to 1 per 10× field) were seen in cingulate gyrus, the only cortical region available for ubiquitin staining.¹³ A careful search of hematoxylin and eosin-stained sections identified no Lewy bodies in other neocortical areas.

Case 2

This 73-year-old right-handed man, a retired tool designer, enjoyed excellent general health until 1986, when he developed a cough and gagged recurrently.

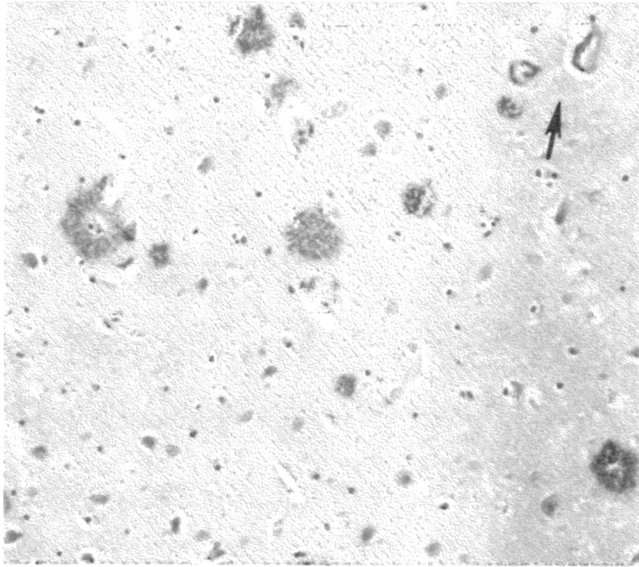


Figure 2A

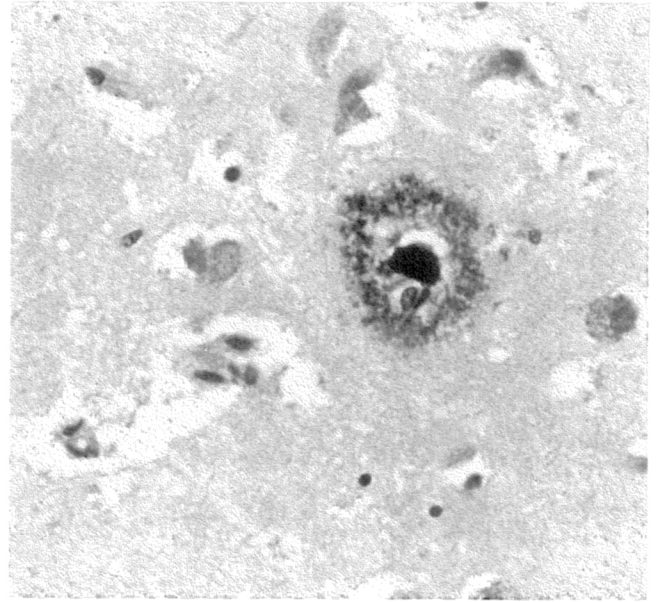


Figure 2B

FIGURE 2

Case 1. A. Cortical section immunostained for A4 amyloid, demonstrating diffuse parenchymal plaques and minimal immunostaining of microvessels (arrow). (Original magnification, $\times 225$.) B. A4-immunoreactive plaque showing a strongly stained central core. (Original magnification, $\times 580$.)

He continued his usual activities, successfully completed his income tax return, and taught a Red Cross class in 1987. Soon after, his speech became "garbled." Neurologic and dementing diseases are absent from the family history.

In 1988, a neurologic consultant described him as inattentive and distractible. His speech was hesitant, stammering, and mildly dysarthric, although he spoke in complete sentences, repeated normally, and adequately followed commands. He was fully oriented and knew the President, Vice President, and Governor. He could not perform similarities. His thinking was concrete, and he perseverated in verbal, written, and motor responses. The gag reflex and muscle stretch reflexes were hyperactive, and a snout reflex was present. Tone, cerebellar function, and gait were normal.

Laboratory studies, including electrolytes, blood glucose, blood urea nitrogen, thyroid function tests, serum protein electrophoresis, ceruloplasmin, Lyme titer, antinuclear antibodies, and syphilis serology were normal or negative. There was a mild microcytic anemia. A T₂-weighted head MRI study demonstrated moderate atrophy and no significant areas of signal enhancement in the periventricular white matter (Figure 3). A waking EEG showed low-voltage

fast background rhythms. In drowsiness, symmetrical theta activity appeared interspersed with runs of intermittent bifrontal activity lasting several seconds. Brain-stem auditory evoked potentials and somatosensory evoked potentials showed no definite abnormalities.

Within a few months, he could no longer manage his checkbook or bills. His capacity to speak degenerated. Most of his utterances were unintelligible, although he continued to drive and bicycle without losing his way. When eating, he coughed and choked, more so with liquids. During a radiographic swallowing study, he did not aspirate but swallowed infrequently and made little attempt to clear his mouth of food. He became dehydrated, confused, and agitated. When treated with haloperidol, he developed severe parkinsonism. These events prompted a hospitalization for gastrostomy tube placement in September 1988.

Following haloperidol withdrawal, he was alert and hypophonic. He did not speak spontaneously. He inconsistently mumbled his name but could not repeat words or sentences. He demonstrated micrographia and marked perseveration both in writing and copying designs and could not follow simple commands. He had difficulty shifting his gaze from

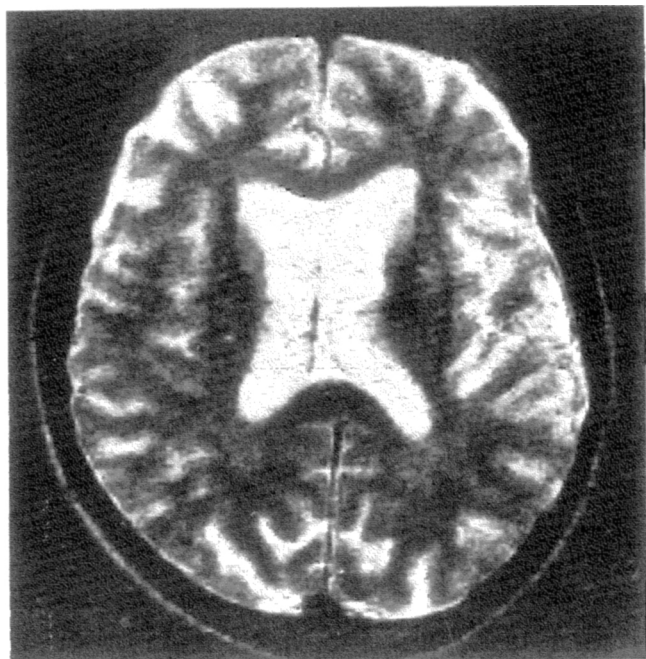


Figure 3A

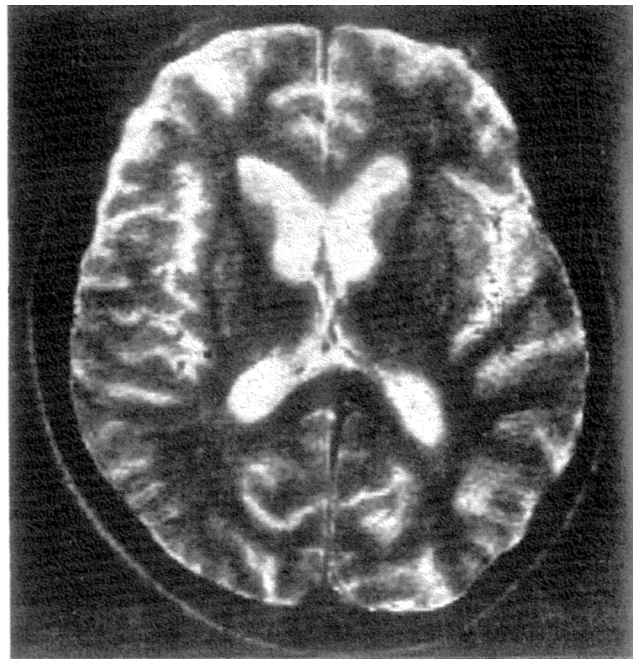


Figure 3B

FIGURE 3

Transverse T₂-weighted MRI scans of case 2 show moderate atrophy.

one target to another. When visually occupied, he ignored verbal or tactile stimuli. There was no evidence of spatial neglect. Spontaneous eye movements were slow, without definite gaze paresis. Gait and turning were normal aside from diminished arm swing. Muscle stretch reflexes remained hyperactive. Plantar responses were flexor. Brisk jaw jerk, suck, snout, grasp, and glabellar tap reflexes could be elicited. Tone was normal, and there was no focal weakness. Routine studies of cerebrospinal fluid were normal. An EEG demonstrated diffuse slowing in the theta range, with scattered low-voltage delta waves.

His condition stabilized, allowing discharge to a nursing home, where 2 months later he succumbed to an acute bowel obstruction and aspiration pneumonia.

Pathology

The general examination identified an obstructing adenocarcinoma of the sigmoid colon, with colonic perforation, and a solitary liver metastasis.

Neuropathology

The brain weight of 1130 g was associated with moderate gyral narrowing and thinning of the cortical ribbon in the frontal, central, and parietal areas. The lateral ventricles were moderately dilated. Subcorti-

cal structures appeared normal. Hematoxylin and eosin- and Bielschowsky-stained sections identified vacuolization of upper cortical layers, mild neuronal loss, astrocytosis, and many NP with the highest counts (19 to 30 per 200× field) in the orbitofrontal and inferior temporal regions. Most NP were diffuse, and a few had dense amyloid cores. Immunostaining demonstrated A4 positivity of NP, as in case 1. Throughout neocortex there were capillaries with A4-positive material in their walls, which in some cases appeared to be exuding from the wall into the parenchyma (Figure 4A). Rare A4-positive amyloidotic arterioles and venules were encountered in the subarachnoid space.

In Bielschowsky-stained sections, moderate to high densities of diffuse NP were observed in the caudate nucleus, putamen, and thalamus (up to 30 per 200× field). None of these structures had conspicuous neuronal loss or astrocytosis. The substantia nigra showed mild loss of neurons and tissue pigment.

In hippocampus and subiculum, NP and NFT were present in small numbers compatible with the patient's age (Figure 4B). Sommer's sector appeared to be intact. Immunostaining of neocortex, hippocampus, amygdala, hypothalamus, midbrain, and medulla with antiubiquitin, Ab 39, and Alz 50 dem-

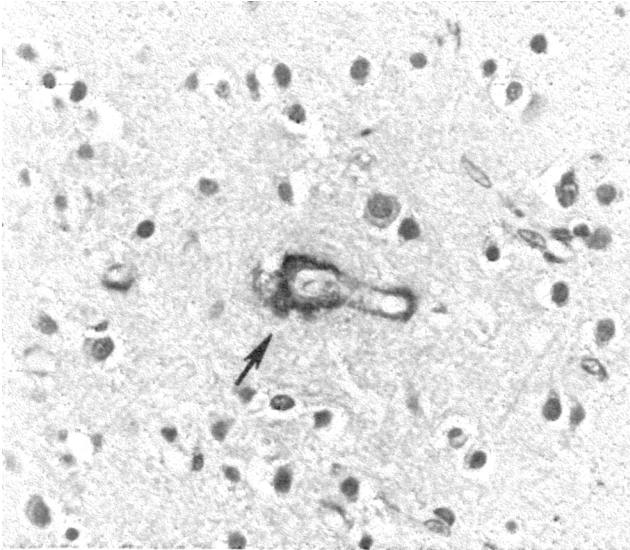


Figure 4A

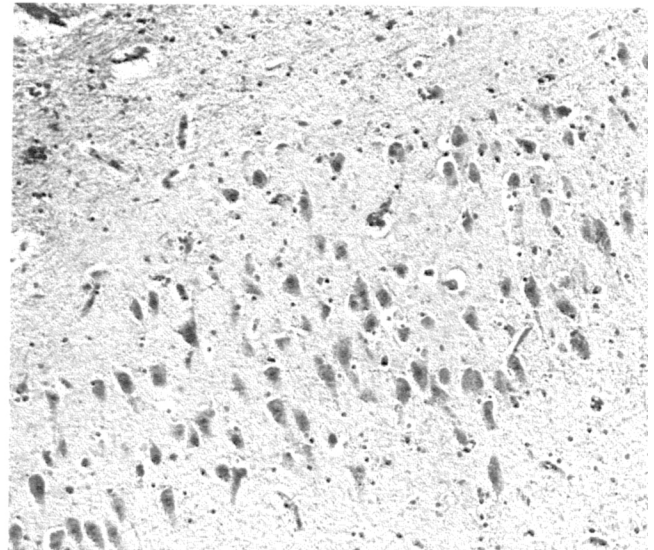


Figure 4B

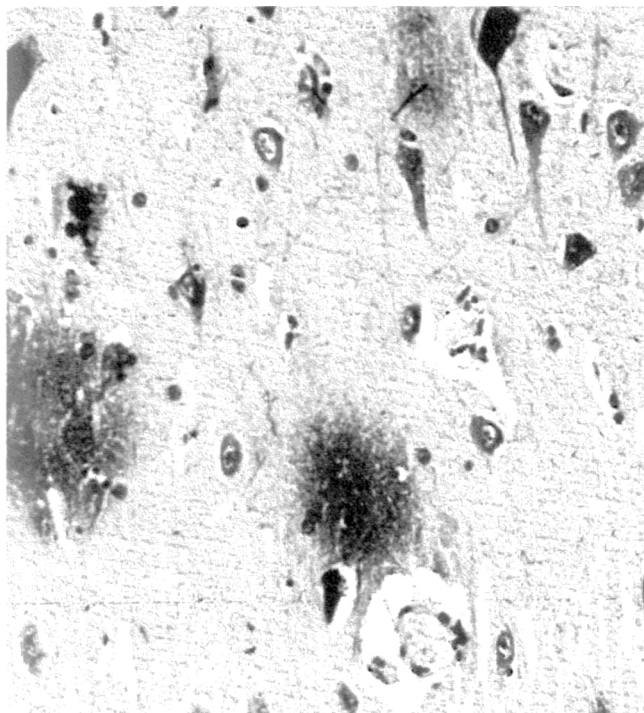


Figure 4C

FIGURE 4
 Case 2. **A.** Prominently A4-immunostained cortical capillary. Along one edge, A4-reactive amyloidotic material seems to be diffusing from vessel wall into parenchyma (arrow). (Original magnification, $\times 580$.) **B.** Hippocampal section demonstrating good preservation of the pyramidal cell layer compared to **C**, the usual hippocampal appearance in patients with "classic" Alzheimer's dementia syndrome. Numerous diffuse NP and NFT are evident. (Bielschowsky stain; original magnification, $\times 200$ in **B**, $\times 400$ in **C**.)

onstrated no cortical or subcortical Lewy bodies and few NFT limited to amygdala.

Discussion

In the first case, clinical features including parkinsonism, visual hallucinations, and fluctuating aware-

ness in the presence of relatively preserved insight, language, and memory distinguish this patient from classic AD. The distinctive neuropathologic features, including preservation of cortical neurons and hippocampus, absence of NFT, and lack of atrophy, similarly deviate from the usual postmortem find-

ings in AD. The feature common to both is an abundance of A4-immunopositive neocortical NP in sufficient numbers to fulfill Khachaturian's diagnostic criteria. Yet differences are more conspicuous than similarities, and disorders other than AD may more closely resemble case 1 clinically and neuropathologically.

Two of four patients described by Burkhardt et al have striking clinical similarities to the patient described here.¹⁴ Both had visual hallucinations, distractibility, perseveration, and myoclonus. One demonstrated wide fluctuations in level of alertness. All four cases had numerous classic Lewy bodies in many cortical and subcortical sites by hematoxylin and eosin and by Bodian staining, and a scarcity of NP. Hence the name diffuse Lewy body disease. Sparing of the hippocampus and minimal or absent cortical atrophy parallel the findings in our case. In identifying a related syndrome, Hansen et al introduced the concept of Lewy body variant of AD.¹⁵ In their series of 13 patients, all had numerous cortical NP accompanied by widespread distribution of Lewy bodies in cortex and subcortical regions, associated with medial temporal spongiform changes. Half had NP but few NFT in the hippocampal region, while in the others, hippocampus was spared. Many had symptoms of parkinsonism; none had delusions.

Immunocytochemical studies suggest that Lewy body variant plaques do not contain the paired helical filament-immunopositive dystrophic neurites commonly encountered in AD.¹³ This finding appears to have been duplicated for the NP seen in both our patients and in the normal aged brain.¹⁶ In a similar group of 14 patients, Perry et al emphasized the presence of hallucinations, extrapyramidal features, and fluctuating confusion, reminiscent of our patient. Compared to AD controls, these patients had a similar density of A4 antiserum-positive NP but smaller numbers of NFT.¹⁷ The small numbers of subcortical and rare cortical Lewy bodies identified by ubiquitin staining in our case are of uncertain diagnostic significance, since they have also been recognized with traditional stains in AD and normal aging, as well as in Parkinson's disease.¹⁸ In Lewy body disease, cingulate gyrus often has the highest density of Lewy bodies, while cell loss and depigmentation are characteristic in the substantia nigra.^{15,16}

Although our first patient does not have Lewy body disease neuropathologically, in a clinical spectrum ranging from AD to AD Lewy body variant and Lewy body disease, this case most resembles

the latter entities and shares some of their neuropathologic features.

Case 2 bears little clinical resemblance to these diseases or to case 1, despite many common neuropathologic findings, particularly the high cortical NP counts and hippocampal preservation. Moreover, a search of the literature for a clinical likeness of case 2 proved unrewarding. The closest approximation located by the authors is a report of Lidov et al, who describe a middle-aged man with progressive medullary failure in the absence of dementia.¹⁹ This 10-year illness commenced with bulbar dysphagia, compared with probable pseudobulbar palsy in our patient. The absence of NFT in neocortex and presence of NP in cingulate and temporal cortex as well as hippocampus resemble the neuropathologic features of case 2. At variance were neurofibrillary changes in brain-stem nuclei and hippocampus that reacted with antiphosphorylated neurofilament antibody, suggesting the presence of tau protein, a major component of AD NFT.

An alternative clinical model in case 2 is the possible association between colon cancer and degenerative brain disease. The authors have identified two additional cases, neither of which had specific microscopic features. Ball's patient suffered from 6 years of progressive dementia beginning at age 57 years. The brain showed isolated cell loss and gliosis limited to inferior temporal gyrus, hippocampus, and amygdala. The patient had rectal adenocarcinoma and transitional cell bladder cancer, both of which were discovered in the last 9 months of life.⁴ Verity et al describe a 78-year-old man with progressive dementia who died at age 82 years from metastatic colon cancer and a bowel obstruction. The major neuropathologic finding was limbic sclerosis, especially of the hippocampus, in the absence of NP and NFT.²⁰

Specific microscopic neuropathologic change, atypical dementia, and remote neoplasm is reported in a 49-year-old woman with metastatic carcinoma of the breast and uterus who suffered a progressive confusional syndrome during the last 5 months of life. The postmortem brain demonstrated numerous cortical NFT, nerve cell chromatolysis, and the absence of senile plaques.²¹ The concurrence of atypical dementia, NP deposition, and remote malignancy has not been previously reported. The novel associations in these reports and the present case expand on earlier observations of limbic encephalitis and other paraneoplastic diseases of the brain.²² The possible causal association deserves further scrutiny.

Clinical AD Versus Neuropathologic AD: Inconsistencies and Paradoxes

Even when applied to "typical" cases, accepted diagnostic criteria may prove inadequate. Careful observations demonstrate that the AD syndrome and AD neuropathology do not always coincide. AD syndrome occurs in patients who have NP but no NFT in neocortex. All had hippocampal neurofibrillary change.²³ Some nondemented patients have post-mortem neuropathologic changes compatible with the diagnosis of AD.^{3,7,8} Moreover, a subgroup of patients with AD syndrome had low NP or NFT counts in either cortex or hippocampus. In these demented patients, loss of large neurons rather than NP and NFT densities best correlated with the severity of intellectual decline.⁸

Additional studies demonstrate a disparity between clinical and neuropathologic AD. In a series of 25 patients with AD meeting NINCDS ADRDA criteria,¹ Risse et al describe three cases with A4-positive immunostained cortical NP but no NFT in hippocampus. In two of these cases, low cortical plaque counts of 6 and 7/mm² precluded a neuropathologic diagnosis of AD. Six other cases demonstrated none of the neuropathologic features of AD.²⁴ Bird et al report two brothers with familial AD and schizophrenia-like symptoms that progressed to a dementia with rigidity and tremor. Both autopsied cases had widespread cortical and subcortical NFT but no NP, one had complete sparing of the hippocampus, and the other had granulovacuolar degeneration.²⁵ Indeed, the neuropathologic features in these cases more closely resemble the "pure tangle" diseases, such as dementia pugilistica, in which NP are absent.

Further evidence for the clinical and neuropathologic heterogeneity in AD is found in progressive focal syndromes that have been associated with the neuropathology of AD. Thus "typical" AD changes may be atypically distributed as in reports of Balint's syndrome,^{26,27} Gerstmann's syndrome,²⁸ nonfluent aphasia,²⁹ and left hemiparesis.³⁰

The evident dichotomy between AD as a clinical syndrome and AD as a postmortem diagnosis raises several conceptual issues. Is AD a single entity or many? Might NFT and NP represent a generic "injury response," and does focal damage in AD, particularly of hippocampus, suggest a pathogenesis? Examination of disorders that share some features of AD may provide a means to investigate these points.

NFT are found in dementia pugilistica, Guama-

nian parkinsonism, amyotrophic lateral sclerosis dementia complex, subacute sclerosing panencephalitis, progressive supranuclear palsy, Parkinson's disease, and Down's syndrome. Immunocytochemical studies have identified antigens common to NFT in all of these conditions.^{31,32} Antigens characteristic of NFT are also found in other intracellular inclusions. Anti-tau antibodies label Pick bodies. NFT components such as myelin-associated protein and ubiquitin are present in Lewy bodies.³³ These observations suggest that various disease mechanisms lead to similar or identical alterations of neurofilament and microtubule components.

The presence of cortical A4-positive immunostained amyloid plaques is not unique to AD. These lesions are found in the brains of normal elderly humans and several species of aged mammals.³⁴ High densities of NP are described in the resected temporal lobes of two nondemented patients with temporal lobe epilepsy.³⁵ Moreover, the links between amyloid accumulation, NP formation, and the AD syndrome remain incompletely defined. Immunocytochemical studies with monoclonal A4 antibodies identify this polymerized protein throughout AD brains, including cerebellum, where NP are usually not found.³⁶ Massive A4 amyloid deposition occurs both in cortical and meningeal vessels and in primitive plaques in Dutch cerebral amyloid angiopathy, a condition initially manifested by intracerebral hemorrhage rather than by dementia.^{37,38}

The recent application of immunocytochemical techniques to AD and normal aged brain suggests several differences in the antigenic component of NP in these two conditions. Widespread A4 amyloid deposition in the brains of some aged normal individuals and in demented individuals with AD change is distinguished in the latter by the presence of tau immunoreactive dystrophic neurites in NP and neuropil.^{16,39} Immunoreactive paired helical filaments are identified in NP adjacent to NFT, and the presence of NFT rather than NP in neocortex appears to be the determinant of dementia.⁴⁰ These observations implicate several mechanisms of A4-positive NP formation in brain and suggest that NP stained by traditional methods may not be an ideal marker for AD.

The severe hippocampal injury of classic AD aligns this disorder with others in which hippocampus is preferentially damaged. These include anoxia, hypoglycemia, domoic acid intoxication, normal aging, and temporal lobe epilepsy.^{4,41-44} Hippocampal neurons are vulnerable to injury by high-dose gluco-

corticoids, and aside from hypothalamus, hippocampus has the highest density of glucocorticoid receptors in brain.^{45,46} Links between these observations and preferential hippocampal (and parahippocampal) injury in AD remain to be determined. Sparing of hippocampus in our cases and in those with Lewy body disease or Lewy body variant of AD suggests that in these disorders, mechanisms of brain injury differ from those that occur in AD.

The failure of our two cases to conform with the currently accepted clinical and neuropathologic criteria for AD has several implications. First, clinical AD is conceptually different from the neuropathologic entity of AD. The two cases reported and those cited indicate that the neuropathologic underpinnings of a stereotypic dementia syndrome can be quite variable, and conversely, the neuropathologic findings associated with AD may be expressed in life by a variety of illnesses or no illness. Second, the singular presence of either NFT or NP in a number of clinical syndromes and diseases suggests that mechanisms producing these lesions may be independent of one another. NP and NFT may reflect the end result of a variety of insults. Third, current clinical and neuropathologic criteria for AD are excessively broad and thereby may embrace a spectrum of disease entities that have yet to be appreciated.

These cases and others emphasize the need for meticulous clinical definition of dementing illnesses, with rigorous laboratory and neuropathologic correlation. Better definition of borderline cases will facilitate understanding of the more common dementing syndromes. Recognition of the clinical and neuropathologic heterogeneity of Alzheimer's disease is essential for the eventual understanding of this disorder.

Acknowledgments

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