

Alzheimer Staging

General statements to be included in your Alzheimer's autopsies (under micro)

1. Alzheimer disease is a heterogeneous clinicopathological entity. Thus, only probabilistic statements about the presence or absence of dementia can be made based on pathological findings alone, and postmortem brain pathology can only be inferred when a progressive dementia has been documented in a living elderly individual.
2. Since dementia may arise from more than one disorder, more than one pathological process may contribute to dementia.
3. The NIH Alzheimer's disease staging worksheet can be found in this patient's autopsy file or as a permanent bound record, located in the pathology office- NIH, Bldg. 10, room 2N212.

Include the relevant statement of the following (in your micro):

1. The likelihood that Alzheimer Disease accounts for dementia is high when the postmortem brain shows both neuritic plaques and neurofibrillary tangles in neocortex (CERAD= frequent, Braak stage V or VI)
2. The likelihood that Alzheimer Disease accounts for dementia is intermediate when there are moderate neocortical neuritic plaques and neurofibrillary tangles in limbic regions (CERAD= moderate, Braak= III or IV)
3. The likelihood that Alzheimer Disease accounts for dementia is low when there are neuritic plaques and neurofibrillary tangles in a more limited distribution and or severity (CERAD=infrequent and Braak I or II).
4. The stains used to confirm the diagnosis included silver, β -amyloid, tau, and ubiquitin on relevant sections. All sections were stained with hematoxylin and eosin. The entorhinal cortex was used for Braak staging while the _____ lobe cortex was used for CERAD staging.

Additional items to include in your micro:

1. describe all infarcts, and their vascular territory if relevant, categorize to ischemic, anoxic or ischemic/anoxic as indicated. Date the infarct (s).
2. describe all findings that are not plaques, tangles or amyloid (ex. hemorrhage, meningiomas, metastases, metabolic encephalopathy)

Staging--Braak

Braak Amyloid scale

- A initial deposits limited to basal portions of the isocortex
- B amyloid in virtually all isocortical association areas
- C all area of the isocortex including sensory and motor core fields, with increasing numbers of amyloid deposits

Braak Neurofibrillary changes

I-II neurofibrillary tangles and neuropil threads are limited to a single layer of the transentorhinal region

III-IV severe involvement of the entorhinal and transentorhinal layer pre- α

V-VI isocortical destruction

***refer to Braak diagrams for reference to locations of entorhinal regions and involvement

staging-CERAD

Demographic data

postmortem interval _____

race _____ (white, black, asian, hispanic, other, unknown)

clinical category 1= chronic progressive dementia diagnosed clinically as AD

2= control subject, normal cognitive function

3= other dementing illness _____

approximate duration of dementia _____

History

Circle the relevant clinical diagnoses:

Alzheimer's disease

vascular dementia

Parkinson's disease

Heart disease

Hypertension

Stroke/TIA

Seizures

Thyroid disease

Diabetes

Alcoholism

Drug intoxication

Head injury

B12 deficiency

affective disorder

psychiatric disorder

neurological disease

medical disease

specify _____

Autopsy major findings, systemic

1. _____

2. _____

3. _____

Gross Exam of Brain— see gross exam sheet

Microscopic evaluation of hippocampus and adjacent regions-

Age related plaque score, using section of frontal, temporal or parietal cortex with maximum involvement

age of patient at death	frequency of neuritic plaques			
years	none	sparse	moderate	frequent
<50	0	C	C	C
50-75	0	B	C	C
>75	0	A	B	C

section used= _____

code for above chart:

0= no histological evidence of AD

A= histological findings uncertain of AD

B= histological findings suggest AD

C= histological findings indicate AD

Lewy body assessment (bilateral substantia nigra, pons medulla and neocortex)

0= no Lewy bodies

1= 1 or 2 Lewy bodies

2= 3-5 Lewy bodies

3= more than 5 neurons with Lewy bodies

***Refer to CERAD worksheets for final coding and key

Final Braak Stage= _____

Final CERAD AD Stage= _____

Additional CERAD Neuropathology diagnosis (PD, Vascular, other).

1 _____

2 _____

3 _____

The brain of this patient was examined to determine the cause of his/her dementia. Detailed clinical history was not available. The cause of dementia in this case was Alzheimer's Disease.

COMMENT ON ALZHEIMER'S DISEASE: Alzheimer's Disease (AD) is the most common cause of dementia in the industrialized nations of the west. The clinical course of AD has been succinctly summarized by Tomlinson and Corsellis (1). AD lasts an average of five years, but may run a short course of only a few months, or last as long as 21 years. It typically begins with impairment of recent memory and is usually noted first by those closest to the patient. Early in the course, patients are typically listless and apathetic but may be restless or excited and have delusions or hallucinations. As the disease progresses, patients become increasingly confused and disoriented and lose the ability to care for themselves. Agnosia and apraxia may occur, and there may be signs of pyramidal or extrapyramidal involvement. In time all memory is lost, friends and relatives can no longer be recognized, and speech becomes incomprehensible. In the terminal stage, patients often become incontinent and frequently waste away.

The enormous social and economic costs of AD are well documented. In the United States, this disease affects roughly 10 percent of the population above the age of 65, and nearly 50 percent of those over 85, according to a recent community-based study (15). AD is the most frequent cause of institutionalization in nursing homes and costs an estimated six billion dollars per year (2).

There are three patterns of inheritance in AD (3). In most cases, AD is sporadic, and there is no evidence of involvement in relatives. In about 30-40 percent of cases of AD, at least one relative has a similar disease, but the inheritance does not follow any classic pattern. A

rare form of AD has been described which is inherited as a simple Mendelian dominant. While there is an increased risk of AD among the first degree relatives of patients who show AD at a young age, this increased risk is relatively small compared with the overall prevalence of AD.

At gross examination, the cerebral gyri of patients with AD usually show some degree of atrophy with a corresponding widening of the sulci and ventricular enlargement (3). The overall brain weight typically is reduced and in the range of 950-1050 gm. There is considerable overlap in the gross appearance of AD brains and those of age-matched controls, so the gross changes are not diagnostic. Occasionally, the brains of patients with AD show marked asymmetric atrophy that falsely suggests a diagnosis of Pick's disease.

The major histopathological changes seen in AD (1,3) are a.) an increased number of neuritic plaques throughout the hippocampus and cerebral cortex; b.) an increased number of neurofibrillary tangles in neurons of the cerebral cortex and hippocampus; c.) increased granulovacuolar degeneration in the hippocampus; and d.) increased numbers of Hirano bodies in the hippocampus. In about 50 percent of cases, there is amyloid infiltration in the walls of blood vessels, a change referred to as amyloid angiopathy because it is demonstrated by immunohistochemical staining for cerebrovascular amyloid protein (4G8). The degenerating neurites in neuritic plaques stain positively with silver stains. Often these plaques have a central amyloid core that stains positively with 4G8. The number of neuritic plaques present correlates reasonably well with the severity of dementia as measured on mental test scores. Recent research at our institution has focused on the production and metabolism of this unique amyloid protein. It had previously been shown that this protein is encoded by a gene on chromosome 21 (15), a discovery that was particularly significant as patients with Down's syndrome (trisomy 21) invariably develop AD. While there is no evidence of duplication of this chromosome in AD, we have shown that cells which degenerate in AD are more actively producing messenger RNA derived from this gene (16,17). We have also found soluble derivatives of the amyloid precursor protein in cerebrospinal fluid (18), and our initial assessment of the relative amounts of these derivatives indicates a close correlation with the degree of intellectual impairment.

At the electron microscopic level, neurofibrillary tangles are composed of paired helical filaments (PHFs). Each filament of the pair is 10 nm. in width and wraps around its twin every 80 nm. causing the diameter of the helix to decrease from a maximum of 20-24 nm. to a minimum of 10 nm. every 80 nm. Careful immunocytochemical analysis of these PHFs has shown that they share antigenic determinants with normal neurofilaments and microtubule-associated proteins (4-6). Thus PHFs appear to represent an abnormality of the normal cytoskeleton. It is important to point out that all of the histopathological changes observed in AD also occur to a reduced extent during the aging of non-demented individuals.

Currently, the diagnosis of AD must be made at autopsy and is based on the demonstration of large numbers of neuritic plaques, and/or neurofibrillary tangles throughout the cerebral cortex and hippocampus. Generally accepted guidelines as to the numbers of neuritic plaques and/or neurofibrillary tangles required for the diagnosis of AD in patients of various ages were developed at the National Institute on Aging and the Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer Disease (JNEN October 1997).

In this case, the number of neuritic plaques present in the cerebral cortex greatly exceeds the established guidelines. In the hippocampus, many pyramidal cells contained neurofibrillary tangles and/or were undergoing granulovacuolar degeneration, and there

was increased number of Hirano bodies. Thus, the diagnosis of AD is unequivocal. In the cerebrum, there was a mild/moderate/severe amyloid angiopathy in this case.

Over the past decade, it has become clear that the basal forebrain cholinergic system invariably degenerates in AD (2,7). Comparison of AD brains with those of age-matched controls has shown the following: a.) There is a substantial and consistent decrease in choline acetyltransferase (ChAT) in the cerebral cortex and hippocampus. ChAT, the enzyme that synthesizes acetylcholine (ACh) from choline and acetyl-CoA, is found exclusively in neurons that use acetylcholine as their transmitter. b.) The extent of the decrease in ChAT correlates reasonably well with the number of neuritic plaques and the severity of dementia as measured on mental test scores. c.) ACh synthesis and choline uptake are decreased in biopsy specimens from the cerebral cortex. d.) Acetylcholinesterase (AChE) decreases in the cerebral cortex and hippocampus. AChE, the enzyme that hydrolyzes ACh, breaking it down into choline and acetate, is found in both neurons that release ACh as their transmitter and in neurons that respond to the ACh that is released.

Studies in experimental animals have shown that the major cholinergic innervation to the cerebral cortex and hippocampus is provided by the basal forebrain cholinergic system. This system, which is also referred to as the magnocellular basal nucleus, consists of clusters of large neurons and scattered perikarya located in the medial septum, diagonal band of Broca, and nucleus basalis of Meynert (nbM). In AD, the number of cholinergic neurons in the nbM is consistently decreased (2). The surviving cholinergic neurons more frequently contain neurofibrillary tangles than the neurons in age-matched controls, have smaller nucleoli, and contain less cytoplasmic RNA.

The basal forebrain cholinergic system appears to play a role in the processing of recent memories (2). It seems likely, therefore, that the abnormalities that occur in this system underlie at least some of the symptomatic manifestations of AD. The demonstration, in several clinical trials, that cholinergic drugs cause small, but measurable, improvement in the cognitive performance of patients with AD provides partial support for this concept (8-11). It should be pointed out that the improvement with cholinergic therapy has generally been too slight to be of significant clinical benefit to patients with AD and that there are continuing trials aimed at optimizing this approach.

Neuronal systems other than the basal forebrain cholinergic system also deteriorate in at least some cases of AD. These include the neurons that provide somatostatin to the cerebral cortex, noradrenergic neurons that project from the locus ceruleus to the cerebral cortex, serotonergic neurons within the midbrain, hippocampal pyramidal neurons, and large pyramidal neurons within the cerebral cortex (for recent review, see 12,13). The mechanism(s) responsible for neuronal degeneration in AD and the relationship(s) between neuronal degeneration and the histopathological lesions that occur are poorly understood.

References:

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