Alzheimer Changes in Nondemented Patients Younger than Sixty-Five: Possible Early Stages of Alzheimer's Disease and Senile Dementia of Alzheimer Type

J. Ulrich, MD

Senile plaques (SP) and neurofibrillary tangles (NFT) were found in 38 (74.5%) of 51 unselected brains of nondemented patients who died between the ages of 55 and 64 years. A high proportion (22, or 43%) had only NFTs. These were consistently present in the entorhinal cortex and/or the hippocampus; the olfactory bulb, the amygdala, and the nucleus basalis of Meynert were also occasionally involved. Isolated SPs were seen in only 3 brains (6%); SPs and NFTs coexisted in 13 (25.5%). The distribution patterns of NFTs and SPs differed. NFTs were seen in discrete, mostly single neurons of the structure, already noted, whereas SPs occurred in a more generalized distribution over the base and convexity of the cerebrum. The plaques were usually small (30 μ in diameter) and consisted of delicate fibrillary material. Other types of SP were also seen. The incidence of various types of plaques in nondemented patients is considered to indicate a morphological evolution of these structures.

Ulrich J: Alzheimer changes in nondemented patients younger than sixty-five: possible early stages of Alzheimer's disease and senile dementia of Alzheimer type. Ann Neurol 17:273–277, 1985

The study of the morphology of Alzheimer's disease and senile dementia of Alzheimer type (SDAT) has been based on brains from demented patients or on small biopsy samples of neocortex. Both types of specimen usually exhibit advanced stages of the diseases. It is well known, however, that a considerable proportion of nondemented patients who die between 55 and 64 exhibit Alzheimer type changes in a mild degree [29, 36]. Therefore we studied a series of unselected brains from such patients to identify the anatomical distribution, incidence, and morphological features of the Alzheimer type changes and to compare them with the alterations in clinically expressed Alzheimer's disease and SDAT. It was hoped that the type and distribution of Alzheimer type lesions in these younger nondemented patients might give indications as to a possible environmental factor causing or provoking the disease.

Materials and Methods

Fifty-one brains of unselected patients who died between the ages of 55 and 64 were fixed in phosphate-buffered formalin for 8 to 12 days, when frontal (coronal) slices were cut. Gross changes were noted. Tissue samples from both olfactory bulbs, both basal nuclei (Meynert), and both amygdaloid nuclei were dehydrated and embedded in paraffin. Three blocks were made of each of the hippocampi (anterior, medial, and posterior part), and one block from the gyrus rectus, first frontal gyrus, first temporal convolution occipital convexity, and the calcarine fissure from each side. Sections 5 to 7 μm in thickness were stained with thioflavine-S and hematoxylin-eosin. Thioflavine-stained sections were screened with fluorescence microscopy for the presence of NFTs and SPs. Hematoxylin-eosin–stained sections were used to exclude gross abnormalities such as softenings and tumors and to orient the sections more easily.

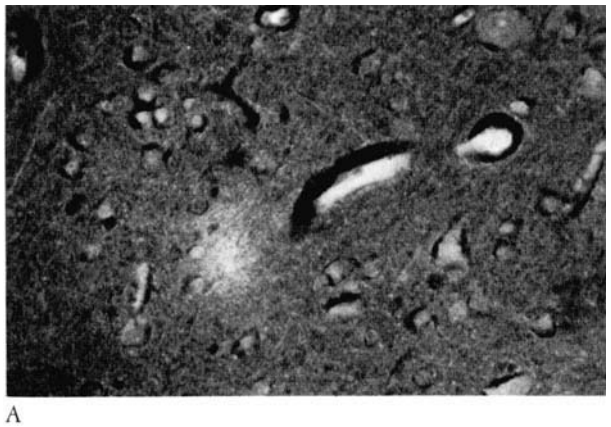
Plaques and tangles were noted and localized. Four types of plaques were classified according to the method of Wisniewski and Terry [38]:

1. Cotton wool–like spherical areas about 50 μm in diameter, in which the single cell processes can hardly be distinguished, but which are clearly distinguished by their fluorescence (Fig 1). Since they look similar to plaques occurring very early in the course of experimental scrapie [30], they are called very primitive plaques.
2. Plaques similar to very primitive plaques, but more distinctly circumscribed, in which single cell processes can be distinguished and which do not have a compact center (Fig 2). These are called primitive plaques.
3. Plaques of the same aspect as primitive plaques, but with a compact center of amyloid (Fig 3). These are called classic plaques.
4. Plaques consisting only of a grain of compact amyloid (Fig 4). They are called burned-out plaques.

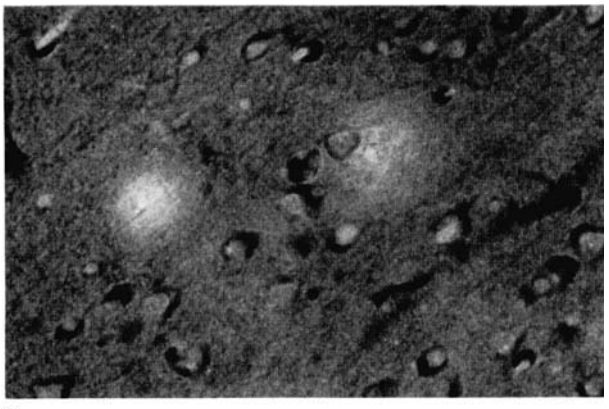
From the Division of Neuropathology, Department of Pathology, University of Basel, CH-4003 Basel, Switzerland.

Received Apr 13, 1984, and in revised form Jun 25. Accepted for publication Jul 10, 1984.

Address reprint requests to Dr Ulrich.



A



B

Fig 1. Very primitive plaques (VPP). (A) Single VPP in entorhinal cortex. (B) Two VPP, closely adjacent to each other. (Both thioflavine-S; ×200 before 13% reduction.)

Results

General Incidence of Alzheimer Type Changes

Only 13 of the 51 brains (25.5%) examined were free of Alzheimer type changes. Of the 38 brains with changes, 22 (43% of all brains) had NFTs only, 3 (6%) had SPs only, and 13 (25.5%) exhibited both types of change. The number of Alzheimer type changes, however, was far below that observed in clinically expressed dementia.

Topography of Alzheimer Type Changes

SPs and NFTs were distributed as noted in Tables 1 and 2. NFTs were nearly always localized in the basal structures of the brain and were found either singly or in a small number of neurons in discrete nuclei. No eosinophilic extracellular tangles [31, 32] were observed. When SPs were observed they were always multiple. They were most often present in the entorhinal cortex, hippocampus, amygdala, and neocortex. The incidence of SPs in the various cortical regions was about equal, with the exception of the calcarine fissure, in which the incidence was about one

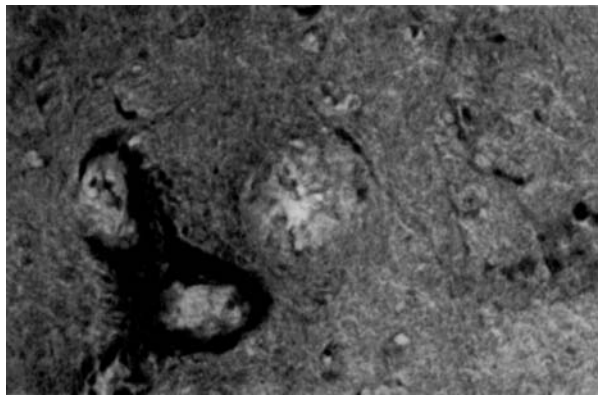


Fig 2. Primitive plaque in nucleus amygdalae. (Thioflavine-S; ×200 before 13% reduction.)

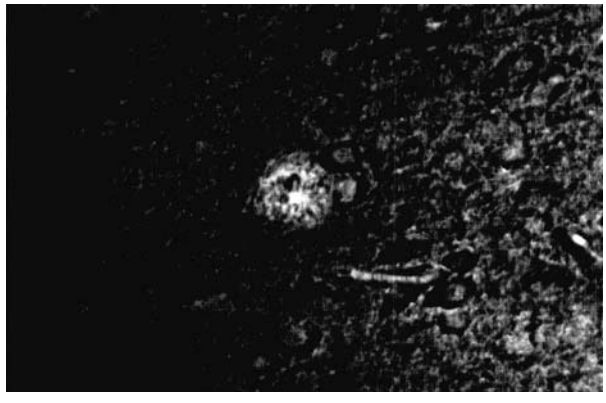


Fig 3. Classic plaque in gyrus rectus. (Thioflavine-S; ×200 before 13% reduction.)

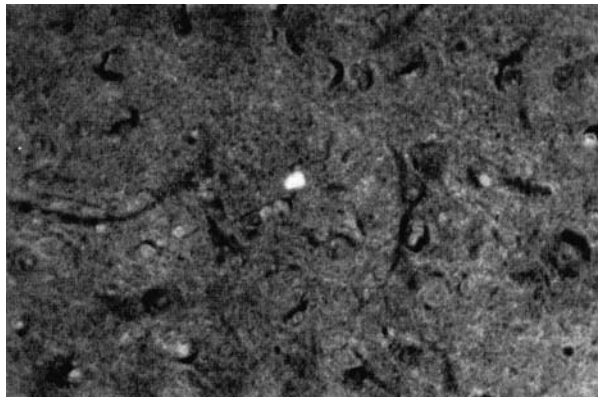


Fig 4. Burned-out plaque in nucleus amygdalae. (Thioflavine-S; ×200 before 13% reduction.)

Table 1. Number of Brains with Alzheimer Type Changes in Various Structures

Structure	Neurofibrillary Tangles	Senile Plaques
Entorhinal cortex	29	10
Hippocampus	12	7
Olfactory bulb	12	0
Amygdaloid nucleus	10	11
Nucleus basalis	7	3
Neocortex		
Gyrus rectus	1[a]	6
First frontal	1[a]	7
First temporal	0	6
Occipital convexity	0	7
Calcarine fissure	0	2
Total neocortex	2	12
One neocortical region	2	6
>One neocortical region	0	6

[a]A solitary neurofibrillary tangle was observed in the sample indicated.

Table 2. Distribution Patterns of Alzheimer Type Changes

Changes	No. of Brains
BRAINS WITH SENILE PLAQUES ONLY	
Amygdalae exclusively	1
Two neocortical areas exclusively	1
Amygdalae both sides (hippocampus both sides, neocortex)	1
Total	3
BRAINS WITH NFTs AND PLAQUES	
Entorhinal cortex only	11
Hippocampus only	5
Entorhinal cortex + hippocampus	18
Total	34
NFTs, SPECIAL DISTRIBUTION PATTERNS	
NFTs in amygdala but in no other structure	1
NFT in nucleus basalis, olfactory bulb, neocortex, not in entorhinal cortex or hippocampus	0

NFT = neurofibrillary tangle.

third that of other sites. Occasionally SPs formed small clusters in the neighboring vessels.

Microscopical Aspects of the Lesions

The neurons with NFTs were not microscopically different from those observed in advanced Alzheimer's disease and in SDAT (Fig 5). Most affected neurons were pyramidal cells of medium size as in the entorhinal cortex, the hippocampus, and the amygdala; mitral cells of the olfactory bulb, and more rarely, its tufted cells were also involved. The largest neurons observed to contain NFTs were the large rounded cells of the nucleus basalis.

SPs were microscopically different from those usually seen in Alzheimer's disease and SDAT. The vast majority were very primitive (Fig 1). They were about 30 μm in diameter and consisted of very fine fluorescent structures. A few brains also contained primitive and classic plaques. In only one instance was a burned-out plaque found (Figs 2–4).

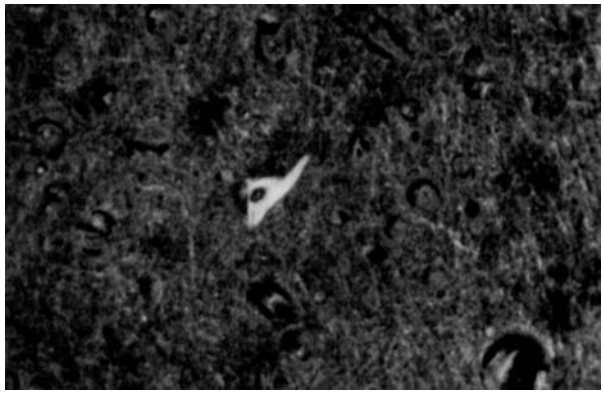


Fig 5. Neurofibrillary tangles in nucleus amygdalae. (Thioflavine-S; ×200 before 13% reduction.)

Discussion

Incidence of Alzheimer Type Changes

The present study revealed Alzheimer type changes in 38 of 51 brains, or more than half of all brains studied, whereas in a prior sample a fourth of the brains were involved [36]. This apparent increasing incidence is undoubtedly the result of both the more sensitive staining method (thioflavine instead of silver impregnation) and the increased number of blocks taken and screened from each brain (18 versus 4).

The proportion of patients who exhibited Alzheimer type changes was much higher than the incidence of SDAT, which is estimated to be about 7% of all persons over the age of 65 [21]. Therefore only a small number of the patients in this study would have become demented. It seems likely, however, that those who eventually do develop SDAT exhibit the early changes of the disease as described here. In the majority of nondemented patients, the changes must be self limiting. In the minority of patients who do develop Alzheimer's disease or SDAT, some qualitatively different process must set in, which might result in the loss of some defense mechanism.

Comparison with Clinically Expressed SDAT, Alzheimer's Disease, and Related Diseases

Brains of mentally normal old persons have been shown to exhibit most of the changes described in the present series [35, 37], but very primitive plaques are now detected for the first time in addition to the previously described primitive, classic, and burned-out types. Our data indicate that the assumption made by Wisniewski and Terry [38] that the SP evolves from the very primitive through the primitive and classic (or mature) to the burned-out type is correct. In most cases of SDAT, the numerical density of both NFTs and SPs increases, but the distribution of these structures remains the same [16, 34, 37]. Nevertheless, in some patients with SDAT, as well as in those with classic Alzheimer's disease and Alzheimer's disease in Down's syndrome [4, 5, 7, 18, 20, 24, 33], NFTs are observed over the entire neocortex except for the calcarine fissure. In these diseases, therefore, there is additional spread of NFTs from the hippocampus, entorhinal cortex, and nucleus amygdalae to the neocortex. Given the multitude of neuronal connections between these structures, it is conceivable that the stimulus for NFT formation spreads from neuron to neuron. The same pattern of NFT spread (not associated with SPs) occurs in boxer's encephalopathy [6].

Different distribution patterns of NFTs are observed in postencephalitic parkinsonism [19] and subacute sclerosing panencephalitis [25]. In these diseases the topographical distribution of NFTs is probably determined by the dissemination of viruses. The same type of mechanism might apply to amyotrophic lateral sclerosis and Parkinson-dementia complex as observed on the island of Guam [14, 15].

NFTs and SPs as Possible Markers of the Entry and Spread of Environmental Agents Causing Alzheimer's Disease and SDAT

The findings of the present study can be interpreted as indications of early cellular aging in certain brain regions. They might also serve to suggest the presence and localization of a causal agent. In these nondemented presenile patients, both SPs and NFTs alone and together were observed, but the distribution of NFTs and SPs was different. These observations suggest that the two lesions may be caused by two different although frequently associated agents. The possibility that a slow virus infection related to that of Creutzfeldt-Jakob disease causes the SPs has been discussed by various authors [3, 11, 13, 17, 22, 23, 28, 39]. Although their pathogenesis is unknown, NFTs are found in some diseases known to be the consequence of viral infections: measles virus, as in subacute sclerosing panencephalitis, and influenza virus in postencephalitic parkinsonism [12, 19, 25]. They might therefore indicate the presence of a virus. Since NFTs were strictly limited to structures of the base of the brain in the presenile brains studied here, it is conceivable that an infectious agent enters the cranium and brain from the nasopharyngeal cavity and spreads there among the structures closely linked with each other by neuronal pathways. Since involvement of the entorhinal cortex or the hippocampus, or both, was sometimes observed in the absence of olfactory NFTs, whereas the opposite was never seen, an invasion from the trigeminal ganglion would be more likely than one from the olfactory mucosa and the olfactory filaments. The same route of invasion by the trigeminal ganglion has been suggested for herpes simplex encephalitis and herpes simplex. It has been suggested as a pathway in the course of SDAT by several authors [1, 2, 8–10, 26, 27].

I am grateful to Dr John Pearson, New York, and Dr Margaret Haugh, London, for critical advice, to Miss M. Nebiker for the photographic work, to Miss A. Hossmann and Y. Müller for technical help, and to Mrs L. Bollag, Mrs J. Lehnherr, and Mrs B. Arpagaus for typing the manuscript.

References

1. Ball MJ: Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved? Can J Neurol Sci 9:303–306, 1982
2. Baringer JR, Swoveland P: Recovery of herpes-simplex virus from human trigeminal ganglions. N Engl J Med 288:648–650, 1973
3. Brown P, Salazar AM, Gibbs CJ, Gajdusek DC: Alzheimer's disease and transmissible virus dementia (Creutzfeldt-Jakob disease). Ann NY Acad Sci 396:131–143, 1982
4. Burger PC, Vogel FS: The development of the pathologic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. Am J Pathol 73:457–468, 1973
5. Constantinidis J: Is Alzheimer's disease a major form of senile dementia? Clinical, anatomical and genetic data. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease: Senile Dementia and Related Disorders (Aging, Vol 7). New York, Raven, 1978, pp 15–25
6. Corsellis JAN, Bruton CJ, Freeman-Browne D: The aftermath of boxing. Psychol Med 3:270–303, 1973
7. Crapper DR, Dalton AJ, Skopitz M: Alzheimer's degeneration in Down syndrome. Arch Neurol 33:618–623, 1975
8. Davis LE, Johnson RT: An explanation for the localization of herpes simplex encephalitis? Ann Neurol 5:2–5, 1979
9. Esiri MM: Herpes simplex encephalitis: an immunohistological study of the distribution of viral antigen within the brain. J Neurol Sci 54:209–226, 1982
10. Esiri MM: Viruses and Alzheimer's disease. J Neurol Neurosurg Psychiatry 45:759, 1982
11. Foncin JF, Cardot JL, Martinet Y, Arnott G: Maladie de Gerstmann-Sträussler-Scheinker. Rev Neurol 138:123–135, 1982
12. Gamboa ET, Wolf A, Yahr MD, et al: Influenza virus antigen in postencephalitic parkinsonism brain. Detection by immunofluorescence. Arch Neurol 31:228–232, 1974
13. Hayek J, Ulrich J: Kuru-plaques in Creutzfeldt-Jakob disease. Eur Neurol 13:251–257, 1975
14. Hirano A: Neuropathology of amyotrophic lateral sclerosis and

Parkinson-dementia-complex on Guam. Proceedings of the Fifth International Congress of Neuropathology, Zürich, 1965. Amsterdam, Excerpta Medica, 1966 (International Congress Series No 100), pp 190–194
15. Hirano A, Ghatak NR, Johnson AB, et al: Argentophilic plaques in Creutzfeldt-Jakob-disease. Arch Neurol 26:530–542, 1972
16. Hirano A, Malamud N, Kurland LT: Parkinson-dementia-complex: an endemic disease on the island of Guam. Brain 84:662–679, 1961
17. Hirano A, Zimmerman HM: Alzheimer's neurofibrillary changes. A topographic study. Arch Neurol 7:227–242, 1962
18. Hooper MW, Vogel FS: The limbic system in Alzheimer's disease. A neuropathologic investigation. Am J Pathol 85:1–20, 1976
19. Ishii T, Nakamura Y: Distribution and ultrastructure of Alzheimer's neurofibrillary tangles in postencephalitic parkinsonism of Economo type. Acta Neuropathol 55:59–62, 1981
20. Jamada M, Mehrain P: Verteilungsmuster der senilen Veränderungen im Gehirn. Arch Psychiatr Nervenkr 211:308–324, 1968
21. Katzman R: The prevalence and malignancy of Alzheimer disease. Arch Neurol 33:217–218, 1976
22. Krücke W, Beck E, Vitzthum HG: Creutzfeldt-Jakob-disease. Some unusual morphological features reminiscent of kuru. Z Neurol 206:1–24, 1973
23. Kuzuhara S, Kanazawa I, Sasaki H, et al: Gerstmann-Sträussler-Scheinker's disease. Ann Neurol 14:216–225, 1983
24. Malamud N: Neuropathology of organic brain syndromes associated with aging. In Gaitz CM (ed): Aging and the Brain. New York, Plenum, 1972, pp 63–87
25. Mandybur T, Nagpaul AS, Pappas Z, Niklowitz WJ: Alzheimer neurofibrillary change in subacute sclerosing panencephalitis. Ann Neurol 1:103–107, 1977
26. Mann DMA, Yates PO, Davies JS, Hawkes J: Viruses, parkinsonism and Alzheimer's disease. J Neurol Neurosurg Psychiatry 44:651, 1981
27. Mann DMA, Yates PO, Davies JS, Hawkes J: Viruses and Alzheimer's disease. Reply. J Neurol Neurosurg Psychiatry 45:759–760, 1982
28. Masters CL, Gajdusek DC, Gibbs CJJ: Creutzfeldt-Jakob disease virus isolations from Gerstmann-Sträussler-syndrome. With an analysis of the various forms of amyloid plaque depositions in virus induced spongiform encephalopathies. Brain 104:559–588, 1981
29. Matsuyama A, Nakamura S: Senile changes in the brain in the Japanese: incidence of Alzheimer's neurofibrillary change and senile plaques. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease, New York, Raven, 1978, pp 287–297
30. Moretz RC, Wisniewski HM, Lossinsky AS: Pathogenesis of neuritic and amyloid plaques in scrapie—ultrastructural study of early changes in the cortical neuropil. In Samuel D et al (eds): Aging of the Brain. New York, Raven, 1983, pp 61–79
31. Okamoto K, Hirano A, Yamaguchi H, Hirai S: The fine structure of eosinophilic stages of Alzheimer's neurofibrillary tangles. Clin Electron Microscopy 16:77–82, 1983
32. Probst A, Ulrich J, Heitz PhU: Senile dementia of Alzheimer type, astroglial reaction to extracellular tangles in the hippocampus. Acta Neuropathol (Berl) 57:75–79, 1982
33. Schochet SS, Lampert PW, McCormick WF: Neurofibrillary tangles in patients with Down's syndrome. Acta Neuropathol 23:342–346, 1973
34. Tomlinson BE: The pathology of dementia. In Wells CE (ed): Dementia. Second Edition. Philadelphia, Davis, 1977, pp 113–154
35. Tomlinson BE, Blessed G, Roth M: Observations on the brain of nondemented old people. J Neurol Sci 7:331–356, 1968
36. Ulrich J: Senile plaques and neurofibrillary tangles of the Alzheimer type in nondemented individuals at presenile age. Gerontology 28:86–96, 1982
37. Ulrich J, Stähelin HB: The variable topography of Alzheimer type (AT)-changes in senile dementia. Gerontology 30:210–214, 1984
38. Wisniewski HM, Terry RD: Reexamination of the pathogenesis of the senile plaque. In Zimmerman HM (ed): Progress in Neuropathology. New York, Grune & Stratton, 1973, vol 2, pp 1–26
39. Zarranz JJ, Rivera-Pomas JM, Salissachs P: Kuru plaques in the brain of two cases with Creutzfeldt-Jakob disease. J Neurol Sci 43:291–300, 1979