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Neurofibrillary tangle predominant form of senile dementia of Alzheimer type: a rare subtype in very old subjects

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Abstract In a consecutive autopsy series of 580 demented elderly subjects, 256 with the clinical diagnosis of probable/possible Alzheimer's disease (AD), there were 10 cases aged between 80 and 99 years with moderate to severe dementia or confusional state in which neuropathological studies revealed abundant neurofibrillary tangles with predominant involvement of the allocortex (entorhinal region, subiculum, CA 1 sector of hippocampus, amygdala) but no or only very few senile plaques. Small numbers of diffuse deposits of βA4 amyloid protein were present in the entorhinal cortex of 3 and in the isocortex of 5 brains, while neuritic plaques were totally absent. Only a few cases of this "senile dementia with tangles only" or, more correctly, "neurofibrillary predominant type of AD" corresponding to the limbic stage of neuritic AD pathology have been described in the literature. This rare subtype occurring in very old (over 80 years of age) subjects that does not fall within the currently used neuropathological criteria for diagnosis of AD warrants further clinico-pathological documentation.

Key words Dementia · Alzheimer's disease
Neurofibrillary tangles · Limbic Alzheimer pathology

Introduction

The anatomical hallmarks of Alzheimer's disease (AD) are the focal extracellular deposition of βA4 amyloid protein, forming part of the senile plaques (SP) and present in cerebral vasculature, and the accumulation of paired helical filaments, composed of pathologically phosphorylated tau-protein in neuronal perikarya and dendrites, producing neurofibrillary tangles (NFT) and neuropil threads (NT). Both types of lesions, the pathogenic relationship of which is still poorly understood, show various stages of development and accumulate in stereotyped but independent spatial patterns with variable intensity in both cognitively intact aged subjects and demented patients with AD (see [7, 57]).

Current criteria for the neuropathological diagnosis of AD based on (semi)quantitiative assessment of age-related SP and/or NFT scores [36, 45, 58] are subject to considerable variations in reliability between observers [11, 19, 40, 44, 48] and give little information on the degree of cognitive impairment of the affected individuals. Several studies have demonstrated that neuritic AD lesion counts and synaptic pathology correlate better with cognitive decline than does amyloid deposition [1, 4, 28, 35, 37, 38, 39, 47, 49, 52, 57]. According to recent comparative clinico-pathological studies, graded psychostatus also shows a linear correlation to the neuropathological staging of neuritic AD pathology [2, 8] based on the hierarchical spreading of NFT from the inferomedial allocortex via the hippocampus to isocortical association areas [6].

Whereas amyloid deposits in the isocortex associated with neuritic AD changes in the hippocampus/limbic system are frequently observed in cognitively intact aged individuals [1, 15, 49] and particularly in persons aged over 90 years [21, 46], a similar pattern with only few or absent isocortical NFT has been reported in 20–30% of demented AD patients [39, 56]. While this "plaque-only" or "plaque predominant" AD is often associated with the "Lewy body variant of AD" associated with multiple cortical and subcortical Lewy bodies [24], the majority of the brains of demented AD patients show both neocortical SP and NFT ("plaque and tangle AD") [24]. Recently, Ulrich et al. [59] described a group of very old demented subjects whose brains had abundant NFT and/or NT, found almost exclusively in limbic regions [entorhinal region (ERR), hippocampus, amygdala] with none in the isocortex, and with no or only with very small numbers of amyloid deposits. This rare form designated as "senile dementia with tangles only," corresponding to the "limbic" type of AD [7, 33, 45] or to stages III and IV of Braak and Braak [6], does not fall within the current neuropathological criteria

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for AD [36, 43, 58] or has been referred to as "atypical AD" [43]. Only a small number of such cases have been recorded in the literature [13, 21, 23, 25, 42, 43]. Here we report a series of very old individuals presenting this "NFT predominant" subtype of AD observed in a large consecutive autopsy series of demented aged subjects.

Materials and methods

Patient selection

Neuropathological examination was performed on 580 individuals with dementia and over the age of 60 years autopsied at the L. Boltzmann Institute of Clinical Neurobiology, Vienna, from 1989 to 30 June 1994. In 438 of them (75.1%), AD with or without additional pathologies was diagnosed using current criteria. About 20% had been enrolled in the Vienna Prospective Longitudinal study of dementia [33], with repeated clinical and neuropsychological examination; the severity of dementia was scored by the Mini-Mental State (MMS) [20] and other psychometric methods not longer than 4–6 months prior to death. The majority of the patients were clinically evaluated from the case records. Clinical diagnosis was established following the ICD-9, DSM-III-R and the NIA criteria for AD [41]; 265 patients fulfilled the clinical criteria for probable or possible AD, and 241 of these were confirmed at autopsy (90.9% accuracy rate).

Neuropathology methods

All brains were examined according to a standard neuropathological protocol. The fresh brain was weighed and, in a number of cases, halved sagitally. Following fixation in 4% formalin, multiple tissue blocks were taken from the midfrontal, temporal and parietal cortex, anterior and posterior levels of hippocampus including the amygdala, basal ganglia, brain stem, and cerebellum. Paraffin sections were stained with hematoxylin and eosin, modified Bielschowsky and Reusche's silver impregnation [50], and immunohistochemistry for tau and ubiquitin to assess neuritic AD lesions and cortical Lewy bodies; selected sections were stained with an antibody against βA4 and with antibody A-T8 for tau protein subunits (for methods see [9, 37]). Diagnosis of AD was performed by two neuropathologists (C.B., K.J.) using the current age-adjusted criteria [36, 43, 58] and neuritic AD staging [6]. The numbers of NFT were assessed quantitatively in five adjacent serial fields of 1 mm^2. If this was not possible, a semiquantitative assessment was performed using the following scale: 1+, 1–4 NFT/mm^2; 2+, 5–10 NFT/mm^2; and 3+, >10 NFT/mm^2. The consistency between observers was 95% and approached 100% after discussion; the concordance for AD diagnosis between observers was almost perfect [48].

Results

Among the 580 demented elderly individuals, including the 265 patients with probable AD in this consecutive autopsy series, we found 10 subjects whose brains presented abundant NFT almost exclusively involving the allocortex with no or only extremely few amyloid deposits/plaques. There were 8 females and 2 males aged 80–99 (mean 89.6 ± 1.3) years; 7 with a clinical diagnosis of probable AD; 3 of possible AD; almost all were disoriented with moderate to rather severe degrees of dementia. The MMS assessment in 5 patients ranged from 5 to 20; in case 1 MMS remained unchanged during the 3 years prior to death. Two patients each presented additional paranoid symptoms and depression; 2 showed mild extrapyramidal signs (rigidity, gait disorders) without typical Parkinson's disease. The clinical and major neuropathological data are summarized in Table 1. Gross examination of the brains showed considerable atrophy; brain weight ranged from 946 to 1180 (mean 1071 ± 34) g. All brains showed abundant NFT and NT in the ERR involving the superficial pre-alpha, and, less severely, the deep cortical layers; most brains revealed numerous NFT in pre- and prosubiculum, almost all in the amygdala, while 6 showed abundant NFT, and 4 only few NFT and NT in the CA 1 segment of the hippocampus. In at least 5 cases, there were ghost tangles in the severely involved ERR, with subtotal neuronal depletion in the superficial laminae of the ERR in 1 case and in the CA 1 sector of the hippocampus in another case (cases 6 and 9). NFT in the nucleus basalis of Meynert were seen in most cases and in the locus ceruleus in 2 cases. The isocortex showed only a few NFT in 4 cases, mainly in the temporal isocortex, and in 1 case in the frontal, parietal, and occipital cortices. Small numbers of amyloid deposits or diffuse plaques were demonstrated in the ERR in 3, and in the isocortex in 5 brains. These deposits were amorphous and did not contain a central amyloid core or dystrophic neurites stainable by the Bielschowsky method or with ubiquitin antibodies. Five brains showed also mild amyloid angiopathy of the meningeal and cortical vessels. No amyloid deposits were detected in any of the brains in the striatum or cerebellum. Lewy bodies were not observed in any of the cases and regions examined. Lacunes in basal ganglia or old small infarctions were present in 8 brains, while in case 4 (with acute hemiplegia) recent hemorrhagic infarction of the right middle cerebral artery territory was seen. Another brain revealed acute necrosis of the hippocampus making quantification of AD lesions impossible. Using the staging of neuritic AD pathology described by Braak and Braak [6], all these cases were equivalent to limbic stages III (2 cases) and IV (7 cases) ; 1 brain with few isocortical NFT (case. 10) scored stage IV to V, while none of them fulfilled the current diagnostic criteria for AD.

Discussion

The present study describes a group of 10 very old individuals aged 80–99 years, of whom 4 were severely demented, 5 showed moderate dementia and 1 had only mild cognitive changes; however, almost all were disoriented. In 5 patients, psychiatric changes had developed very late in life, whereas in the others the onset of mental deterioration began between 7 and 10 years prior to death and showed only very mild progression. In the oldest patient (case 1), a female aged 99 years with onset of cognitive decline at around age 94, psychostatus remained almost unchanged (MMS 13, 14, 12, 13, and 12 out of 30) during the last 3 years. Two patients were depressed and/or presented with parkinsonian symptoms; two were paranoid. They died from intercurrent pulmonary embolism, coro-

Table 1 Summary of clinical and major neuropathological data. (*NA* not available, *ERR* entorhinal cortex, *HIPCA1* hippocampus CA1 sector, *NBM* nucl. basalis Meynert, *Tic/-Fic/Pic/Occ* temporal/parietal/frontal/occipital isocortex, *AA* amyloid angiopathy, *Amyg* Amygdala, *LC* locus ceruleus, *Sub* subiculum)

Case no.	Age, sex/death (onset)	Clinical diagnosis	Mental status	MMS	Other CNS disorders	Other disorders at autopsy	Brain weight	AD criteria[a]				Neurofibrillary tangles (density per mm² or semi-quantitative staging)						Amyloid depos.		AA	Neuropath. diagnosis	Other CNS lesions
								[36]	[58]	CE [43][a]	[6]	ERR	HIPCA1	Sub	Amyg	NBM	Other	ERR	Isocortex			
1	99M/94	Probable AD	Disoriented	12/30	0	Pneumonia	1100	0	0	0	4	24.0[b,c]	3.0[c]	17.0[b]	2+	10.0	Tic 0.1	0	0	1+	"Limbic AD"	Lacunes striatum, pons
2	91F /82	Probable AD	Disoriented	5/30	0	Myocard. infarct	1075	0	0	0	4	7.0	10.0[c]	13.0[c]	3+	5.0	Lc 1+	0	0	0	"Limbic AD"	Acute anoxia Ammon's horn
3	91F /81	Possible AD	Disoriented	20l30	Depression, rigidity	Pulmonary embolism	1100	0	0	0	3	6.0[c]	5.0[c]	5.0[c]	1+	1+	–	0	0	1+	"Limbic AD"	Lacunes striatum
4	92F /85	Probable AD	Disoriented	17/30	Depression, acute hemi-plegia	Pneumonia, diabet. mell.	1060	0	0	0	3	1+	1+	NA	1+	–	–	0	0	0	"Limbic AD"	Acute hemorrhagic infarct RMCA territory
5	87F /86	Possible AD	Disoriented, moderate dementia	NA	Jacksonian fits	Pulmonary embolism	995	0	0	0	4	20.0[b,c]	8.0[c]	12.0[c]	3+	1+	Tic <1.0	1+	Fic 1+	1+	"Limbic AD"	Small old infarct right frontal cortex
6	82F /?	Possible AD	Disoriented, mild dementia	NA	Tabes (?), optic atrophy	Pulmonary embolism	946	0	0	0	4	30.0[b–d]	3.0	14.0[c]	3+	1+	Lc 1+	0	0	0	"Limbic AD"	Lacunes striatum, no spinal cord lesion
7	90M/86	Probable AD	Disoriented	NA	Alcoholism	Food aspiration, pulm. edema	1140	0	0	0	4	11.0[c]	10.0	10.0	3+	1+	0	1+	0	1+	"Limbic AD"	Lacunes med. thalamus
8	88F /87	Probable AD	"Moderate dementia"	NA	"Parkin-sonism"	Aortic aneurysm	1168	0	0	0	4	16.0[b,e]	5.0	7.0[c]	NA	1+	0	0	0	0	"Limbic AD"	Lacunes striatum
9	80M/77	Probable AD	Disoriented	NA	Paranoid	Pulmonary embolism	1010	0	0	0	4	9.0[c]	17.0[c]	19.0[c]	NA	NA	Tic <1.0	0	0	0	"Limbic AD"	Multiple embolic microscares frontal, temp.-occipital
10	86F /82	Probable AD	Disoriented	14/30	0	Coronary heart dis-ease	1180	0	A1	0	4(–5)	3+[b]	2+	3+	3+	1+	Fic, Pic, Occ 1+	1+	Occ 1+	1+	"Limbic AD" with few iso-cortical NFT	Lacunes striatum

[a] CERAD criteria
[b] Ghost tangles
[c] Neuropil threads
[d] Subtotal neuronal depletion

nary heart disease, or food aspiration. Gross examination of the brain revealed considerable diffuse atrophy. Histologically, all brains except one (case 4) revealed abundant NFT and NT in the hippocampus formation, with predominant involvement of the ERR, subiculum, the CA 1 sector of hippocampus, and nucleus amygdalae, whereas a few isocortical NFT were seen in only 4 cases. No amyloid deposits were found in 7 brains, while a small numbers of diffuse plaques were observed in the ERR in 3, 2 of which (cases 5 and 10) also showed a few diffuse SP in the isocortex. Neuritic plaques were not seen in any of these brains; half of them revealed mild cerebral amyloid angiopathy. Thus, none of these 10 cases, observed in a consecutive autopsy series of 580 demented elderly individuals, 265 with the clinical diagnosis of probable or possible AD, fulfilled the current neuropathological criteria for the diagnosis of definite or probable AD [36, 44, 58]. Using the staging of neuritic AD pathology [6], all of them were equivalent to limbic stages III (2 cases) and IV (7 cases); 1 brain with few isocortical NFT scored stage IV to V. From the morphological point of view, all cases corresponded to the limbic type of AD [33, 45], which has been considered to either represent initial stages of AD [5, 6], or a subtype of AD also referred to as "AD with NFT only" [59] or, more correctly, as "NFT-predominant" AD. It should be distinguished from the frequent "plaque and tangle AD" [25] and the "plaque-predominant" AD [39, 56]. Hippocampal sclerosis recently reported in 26% of a cohort of demented subjects over age 80 years [18] was not observed in the present series.

The majority of demented AD patients show both NFT and SP in the isocortex ("plaque and tangle AD"), while up to 30% are characterized by abundant neocortical diffuse SP with no or only very few NFT [39, 56], findings that are also common in nondemented very old subjects [1, 4, 6, 12, 16, 17, 47, 49, 55]. Isocortical SP are commonly accompanied by neuritic AD changes in the allocortex/hippocampus; these, however, are usually unrelated to the severity of dementia [4, 5]. Very old AD patients often show a more marked decrease in NFT density in allocortex and isocortex than younger AD cases [12, 21, 46], and NFT density in centenarians with AD is usually not different from that seen in non-demented centenarians except in the CA 1 and CA 4 sectors of hippocampus, which show significantly higher numbers of NFT [21, 25, 46]. While allocortical NFT are accompanied by variable numbers of SP in both allo- and isocortex in the majority of brains, there is a small number of very old subjects with various degrees of mental decline, for whom abundant NFT predominantly involving the allocortex represent the prominent neuropathological feature. Ulrich et al. [59] reported 10 brains among about 500 autopsy cases of dementia, with abundant NFT mainly in the limbic structures but with no or only scarce βA4 diffuse SP in 2 of them. Of these 10 cases, 8 were women (84–101 years) and 2 men (75 and 84 years); 5 presented with severe dementia, the others were mildly demented or in an acute confusional state. All cases corresponded to neuritic AD stages III or IV, 2 with a few neocortical NFT to stage IV–V [6], and all would have escaped the currently used diagnostic criteria of AD. In addition to two similar examples of "NFT only AD" [21, 53], only few such cases have been reported: among 12 centenarians Hauw et al. [25] saw 1 case; among 6 mildly demented aged subjects Davis et al. [13] observed a 95-year-old male (CDR 0.5) with few NFT in CA 1, amygdala, ERR, and nucleus basalis of Meynert, with only few primitive SP in insular cortex and amygdala but not in the hippocampus; among 13 autopsy cases of probable AD Mena et al. [42] reported an 80-year-old female with a long history of dementia whose brain showed multiple NFT and Alz-50-positive processes but only a few neuritic plaques among 142 cases of clinically "probable" AD; Mirra et al. [43] observed one single brain showing only NFT, striatal degeneration and no SP, referred to as "atypical AD," which did not fall within the CERAD neuropathological criteria for AD; among 31 autopsy cases aged 96–107 years, including 7 clinically documented AD cases, Giannakopoulos et al. [21] observed one 97-year-old demented woman (case 27) whose brain showed numerous NFT in the ERR, CA 1 sector of hippocampus and subiculum and few NFT in infratemporal isocortex, in the total absence of diffuse SP, whereas 3 non-demented controls ("supernormal centenerians") showed small numbers of NFT in hippocampus and isocortex without any amyloid deposits. In other autopsy series of subjects aged over 80, not a single example of "NFT-predominant AD" has been documented [4, 6, 15, 16, 18, 46].

The observation of this subtype of AD and the well-known fact that NFT in the absence of SP may occur in a variety of CNS diseases, e.g., subacute sclerosing panencephilitis, progressive supranuclear palsy, postencephalitic parkinsonism, Guam-parkinsonism complex, etc. [32, 59, 62], suggests that NFT are neither specific for AD nor may develop solely as a consequence of the presence or neurotoxic action of βA4 amyloid or β amyloid precursor protein (βAPP). They have been shown to result from abnormal hyperphosphorylation of the microtubule-associated tau protein followed by progressive ubiquitination caused by defects in neuronal cytoskeletal protein processing of hitherto unknown origin [2, 14, 22]. Recent studies demonstrate a clear sequence of cytoskeletal changes which occurs in the neuronal processes in the absence of alterations in their immediate surroundings [9]. The neuritic process appears at an early stage to involve the pyramidal neurons of the superficial pre-alpha layer of the transentorhinal and entorhinal region in the anterior parahippocampal cortex, possibly due to enhancement of their high content of βAPP during age-related resprouting [51]. The initially involved pyramidal cells of the superficial ERR are the origin of the glutamatergic "perforant pathway", a major relay and control gate between both the hippocampus and amygdala and many isocortical association areas and limbic circuits [6, 7, 30, 31, 34, 60]. Damage to the ERR affected by neuritic AD pathology will cause synaptic loss in the hippocampus due to its disconnection from isocortical inputs [28, 60]. It, thus, may contribute to early memory or cognitive deficits in both aging

and AD [3, 6–8, 30, 31, 39]. Both the hippocampus with its sectors CA 1 and 4, heavily involved by NFT in aged demented subjects, and the amygdala, which also contains numerous NFT in AD [31, 54, 61], have substantial interconnections and are composed of similar types of cells [7, 10, 13, 61]. The hierarchical spreading of neuritic AD pathology starting in the ERR and spreading subsequently to the hippocampus and isocortex suggests a dynamic process involving selected specific susceptible neuronal subpopulations and circuits [7, 21, 27, 29], probably related to their morphological and neurochemical characteristics, that develops independently of amyloid deposition [7, 15, 26]. Whether the occurrence of prominent neuritic AD pathology almost totally restricted to limbic areas, with only few NFT in isocortex, and only minimal or no βA4 deposits (diffuse SP) in a small number of very old individuals with variable degrees of cognitive impairment represents the initial steps or a rare subtype of AD remains to be elucidated. Further studies will be needed to delineate the "NFT-predominant" form of AD that may escape the currently used diagnostic criteria of AD. These and other "borderline" cases appear worthy of specific clinical and morphological documentation to reduce disagreement in neuropathological diagnosis and clinicopathological evaluation of normal and pathological aging of the human brain.

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