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Senile Dementia with Tangles (Tangle Predominant Form of Senile Dementia)

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Senile dementia with tangles is a sporadic subset of very late onset dementia with preponderance in females over age 80 years. Neuropathology shows diffuse cerebral atrophy with neurofibrillary tangles, often ghost tangles, and neuropil threads almost limited to limbic areas (transentorhinal, entorhinal area, hippocampus – not exclusively sector CA 1 – and amygdala) with only rare and mild involvement of the neocortex, basal ganglia and brainstem (except nucleus basalis and locus ceruleus), absence of neuritic plaques and absence or scarcety of amyloid deposits. This pattern of fibrillary pathology corresponds to Braak stages III and IV or the "limbic" type of Alzheimer disease that is considered the main form in the oldest-old but escapes the current criteria for the morphologic diagnosis of Alzheimer disease. It is distinct from other tau- or tangle-pathology related conditions, e.g. progressive supranuclear palsy, autosomal dominant dementia with tangles, and diffuse tangles with calcification. Very low prevalence of ApoE e4 allele (0.03-0.11%) and higher frequency of ApoE e3 and/or e2 suggest a lack of promoting effect of e4 and a possible protecting effect of e2/3 on amyloidogenesis. Senile dementia with tangles is suggested to be a variant of Alzheimer disease occurring in the oldest-old, but its nosological position within aging disorders of the brain is still controversy.

Introduction

Senile dementia with tangles, first described by Ulrich et al. (91) and later referred to as neurofibrillary predominant form of senile dementia (NFT-SD) (4) denotes a sporadic subtype of progressive dementia in very old subjects that is morphologically characterized by diffuse cerebral atrophy and dominant neurofibrillary tangle (NFT) pathology in the allocortical areas of the inferomedial temporal lobe with only rare and mild involvement of the isocortex corresponding to stages III and IV of neuritic Alzheimer pathology (11). Amyloid deposits are absent in about 75% of described cases, others having a few diffuse plaques and/or mild cerebral amyloid angiopathy. NFTs in the amygdala and nucleus basalis of Meynert, less in locus ceruleus, are seen in most brains, but are absent or extremely rare in other subcortical areas thus not corresponding to diagnostic criteria proposed for progressive supranuclear palsy (PSP) (39, 54). Neuritic plaques, cortical or subcortical Lewy bodies, subcortical gliosis (66) and cerebral calcifications (51) have not been observed (2, 4, 45-47, 91).

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Prevalence

The incidence of this condition in several autopsy series ranges from 0.7% (64), 2% (91) and 3.2% (36) to 5.8% (46) and even 7.7% in a small cohort of mildly demented elderly subjects (62). It was 5.7% in a consecutive autopsy series of 350 cases of probable AD (2). While no such cases have been reported in other autopsy series of subjects over age 80 (6, 22, 23), in small cohorts of non or mildly demented centennarians, cases with hippocampal NFTs in the absence of senile plaques (SP) were observed in 8.3 and 10.2%, respectively (40, 68). Additional single instances of "atypical" AD with hippocampal and neocortical NFTs but no or scarce SP have been reported (21, 37, 48, 77).

Clinical characteristics

Clinically, the condition shows female preponderance of 3-4:1 and is featured by late onset progressive dementia of moderate to severe degree with a duration between 1 and 15 (average 4) years and age at death ranging from 86 to 102 (average 87 to 92.5) years. Severe dementia with Mini-Mental state (MMS) scores between 0 and 14/30 are reported in about one third, the others showing mild to moderate cognitive changes with severe memory disturbances. Many patients are disoriented, depressive or present with delirium, confusion, depression, and other psychiatric symptoms that may develop very late in life. They show very slow progression, as in a female aged 99 with onset of cognitive

Figure 1. Hippocampus of 89 year old demented male showing dense anti-tau immunostaining (blue) in hippocampus and parahippocampus. AT 8 immunostaining

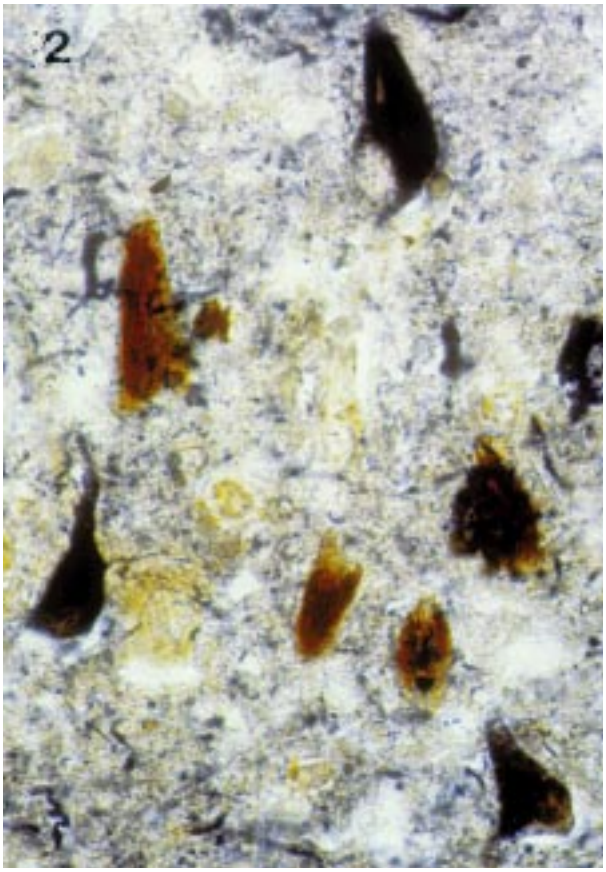


Figure 2. Entorhinal cortex showing tangles with and without ubiquitination (AT-8 - blue; anti-ubiquitin brown). AT 8 and anti-ubiquitin (FPM1) double immunostaining x 1000

decline around age 94, where psychostatus remained almost unchanged (MMS 14 to 12/30) during the last 3 years (4). The majority of these patients has clinical diagnoses of probable or possible AD by NINCDS-ADRDA criteria (60), only very few of vascular or mixed type dementia (2, 4), and all had been hospitalized because of dementia (46). A few patients showed additional extrapyramidal signs (rigidity, gait disorders) (4, 91).

Neuropathology features

Gross examination of the brain shows moderate to severe cerebral atrophy with average brain weight of 1084±109g (2) up to 1120g (91). Histologically, there are abundant NFTs and neuropil threads (NTs) predominantly in the allocortical areas involving the transentorhinal and entorhinal cortex (mainly the superficial pre-alpha but also deep layers), subiculum, praesubiculum, hippocampus (predominantly but not exclusively the CA 1 subfield) (Fig. 1), and amygdala. There are both intracellular and extracellular ("ghost") tangles, the latter often being predominant in the severely involved entorhinal area or in hippocampus (Fig. 2). The morphology, immunoreactivity (tau-positive with preponderance of amino-terminal tau epitopes in intracellular, not in extracellular NFTs, the latter being ubiquitin- and PHF-positive), and ultrastructure of the NFTs (22-25 nm constricted tubules – 47), as well as of the NTs are identical to those in AD (13, 91). NFTs and NTs are either evenly distributed throughout the allocortex with abundant ghost tangles, subtotal neuronal loss and spongy changes in the severly involved entorhinal cortex. A few cases show almost exclusive involvement of the CA1 and CA2 segments of hippocampus where they occupy the majority of pyramidal neurons (2, 4, 91); in others NFTs also occur in CA 3 and CA 4 segments with a few NFTs in the granule cells of the fascia dentata, while in about 20% of our cases, we observed a large number of NFTs in the latter area (Figs. 4, 5). Other severely involved limbic areas are the pre- and prosubiculum, and amygdala, less the subiculum. In 20-30% of the brains, there are small numbers of NFTs and NTs in frontal, temporal, and parietal isocortices, particularly in layers III and V, with preservation of the neocortical association and occipital areas. Ulrich et al. (91) observed argyrophilic grains (9, 10) in 20% of their cases, while we saw these comma-shaped structures in about 66% of our cohort in CA 1 subfield of hippocampus, less frequently and less dense in the (trans)entorhinal region (Fig. 6), but never in isocortex. Argyrophilic, tau-positive oligodendroglial inclusions, termed "coiled

bodies" that have been observed in a variety of neurodegeneration disorders, including PSP, corticobasal degeneration (CBD), AD, etc (16, 27, 28, 70, 99) were seen in about half of our series, particularly in the temporal, and much less in the frontal white matter, even in the absence of cortical NFTs/NTs (Figs. 7, 8). Tau-IR astroglial inclusions, such as "tufted astrocytes" often occurring in PSP and, rarely, in AD (16, 27, 28, 98), and "astrocytic plaques" that have been reported frequently in PSP and CBD (27, 28, 59, 84) were not mentioned in previous case series (2, 4, 48, 49, 91), but were rarely observed on reexamination of personal cases of NFT-SD (Fig. 9).

NFTs and NTs in the nucleus basalis of Meynert are present in most cases, in locus ceruleus in about 25%, and in substantia nigra in 10 to 30% of the reported cases, while they are absent or extremely rare in basal ganglia and brainstem (2, 4, 91). Only Ikeda et al (46, 47) reported NFTs in "the preferential nuclei of the brainstein", however, without detailed data. Amyloid plaques were described in 7/30 available cases (23%) in frontal, parietal, occipital, and entorhinal cortices. These deposits are amorphous and do not contain a central amyloid core nor dystrophic neurites stainable with the Gallyas and Bielschowsky silver techniques or with ubiquitin antibodies (2, 4, 91). No amyloid deposition (98) was seen on extracellular NFTs. In none of the available cases, neuritic plaques or amyloid deposits in striatum and cerebellum have been observed. Amyloid angiopathy of the meningeal and cortical vessels was seen in 10 to 20%. Except for one case in the series of Ulrich et al (91), no cortical or subcortical Lewy bodies were observed. In a large number of brains, small infarctions or other additional vascular lesions of various degree, mainly lacunes in basal ganglia, were present. However, only in one of these cases, vascular lesions were of such an extent to warrant the diagnosis of "mixed type dementia" with coexistance of AD and vascular encephalopathy (2). Hippocampal sclerosis, recently reported in 26% of a cohort of demented subjects over 80 years (24) were seen in 10% of our series (2). Cerebral calcifications and subcortical gliosis have not been reported in any of the brains. Data on the density of synapses or synaptic markers are not available to the best of our knowledge.

From the morphologic point of view, this condition characterized by severe involvement of the entorhinal region, hippocampal formation, and amygdala, with no or very little neocortical and subcortical tau pathology, in the majority of cases corresponds to the "limbic" stages III and/or IV, rarely to stage II (45-47) of neuritic Alzheimer pathology (11), although some of these brains also display variable amounts of NFTs in the CA 2 to CA 4 segments of hippocampus and in the granular cell layer of the fascia dentata that are usually involved only in progressed AD stage V (11). However, considering the scarcely and distribution of isocortical NFTs, none of the published cases scored Braak stage V. Hence, the majority of cases of NFT-SD represents the "limbic" type of AD (11, 49, 67) or group II, the "localized" atrophy type of AD (66). It has been considered to represent incipient AD (8, 12, 13) or a rare subtype of AD in very advanced age (2, 4), although it is considered the morphological main type in the oldest-old showing different distribution pattern of Alzheimer-like lesions from physiologic aging (66). Since neocortical involvement is absent or very mild, Braak stages III and IV fail to meet currently used neuropathologic criteria for the diagnosis of AD (44, 50, 63-65, 88). Although it is well accepted that in AD NFTs are also found in subcortical and brainstem nuclei, in AD with onset over age 70 years, the number of subcortical lesions was not

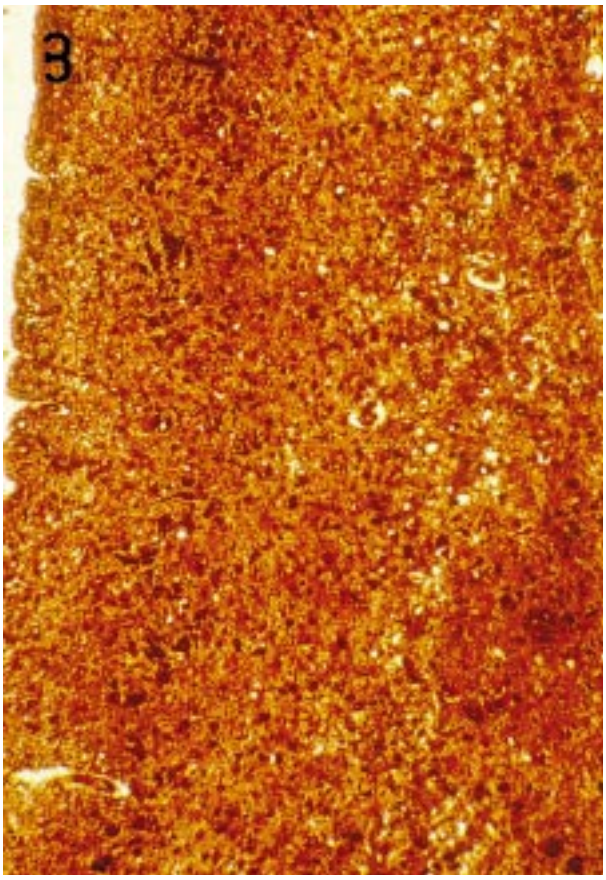
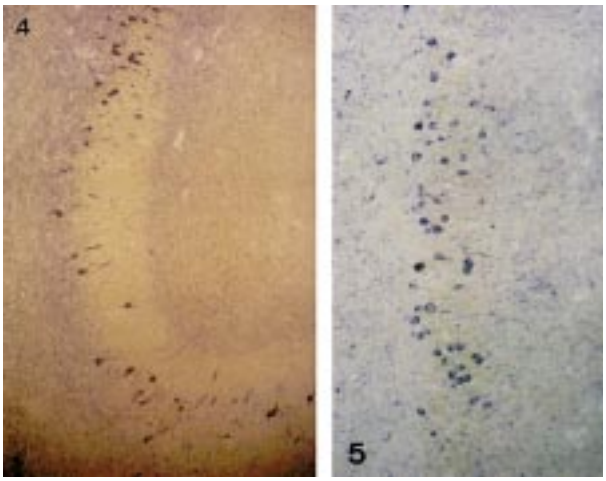


Figure 3. Entorhinal cortex showing ghost tangles in lamina II and spongy destruction of deeper layers. Bielschowsky x 150



Figures. 4 & 5. Fibrillary tangles in granule cell layer of fascia dentata. AT 8 immunostaining x 50

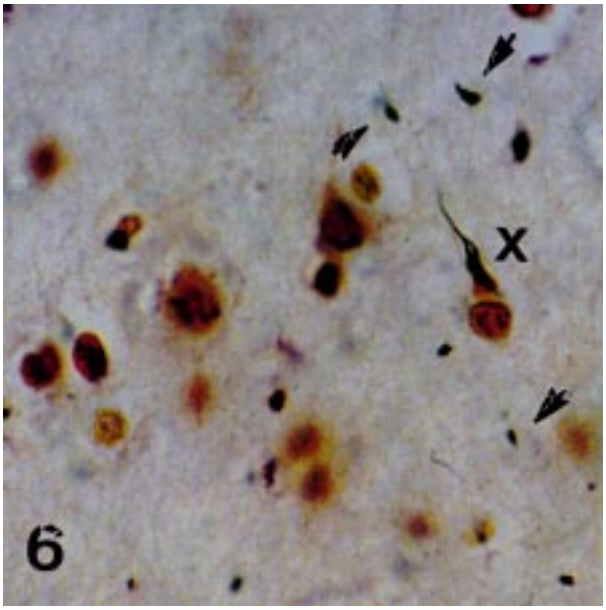


Figure 6. Fibrillary tangle (x) and occasional argyrophilic grains (arrow heads) in CA 1 subfield of hippocampus. Gallyas stain x 850

more than in age-matched controls (68).

Apolipoprotein allele genotypes

ApoE genotyes were reported in two series: The 14 patients of Ikeda et al. (46), had ApoE e2, e3, and e4 allele frequencies of 0.39, 0.50, and 0.11 as compared to 0.03, 0.80, and 0.17 in aged controls. Eight patients had at least one e2 gene and three of these were homozygous for this allele. While there were no e3/4 or e4/4 carriers, three were e2/4 heterozygote. In the group of 18 patients of Bancher et al. (2), the ApoE allele frequences for e2, e3 and e4 were 0.11, 0.86, and 0.03, respectively; 78% were homozygous for e3/3, one for e2/2, two were e2/3, and only one was e3/4 (5.5%). This was highly significantly different from Caucasian AD patients of all age groups or in octogenarians and from cases with Braak stages IV, but did not differ from pooled and very old controls and from AD in nonagenarians and PSP (Table 1). Whereas ApoE e4 allele is increased in late onset AD as compared to controls mainly at the expense of e3 (18, 74, 79, 80), the inverse is true in NFT-SD: there is an increase of e3 at the expense of e4. While the Japanese case series showed a strong increase of ApoE e2 (46), this was not seen in a European sample (2), which could be due to ethnic factors (15, 26) or to the small sample sizes.

The increase of ApoE e3 at the expense of low e4 in this subset of very old demented subjects differing from age-matched AD but neither from nonagenarian AD patients nor from age-matched controls is striking. It supports 1. the molecular genetic and morphologic similarities between oldest-old (centennarians) with AD and without dementia except for higher numbers of NFTs in CA1 and CA4 sectors of hippocampus (30, 36, 65, 67). 2. suggests that the absence or scarcety of Aβ deposits in this condition may be related to the absence of e4 suggested to promote amyloidogenesis or Aβ fibrillogenesis (1a,18, 57), while ApoE e3 and 2 may have a protective effect against amyloid formation (47, 53). Both lesion types, Aβ deposits and NFT, can occur independently in quantity and distribution patterns in both aging brain (11, 12, 49) and other disease conditions (5, 85). In addition, there is statistically significant independence of the development of these two types of lesion in the hippocampus in AD (95), supporting the notion that amyloid deposits and neurofibrillary (tau-related) pathology can be driven and modulated by different pathogenic factors.

Differential diagnosis

NFT-SD is to be distinguished morphologically from the majority of AD cases showing both neocortical SP and NFTs ("plaque- and tangle AD") (11, 38, 44, 88, 95), and from the "plaque-only" or "plaque-predominant" type of AD characterized by abundant neocortical diffuse plaques with limbic but no or only very few neocortical NFTs (19, 38, 86), often associated with cortical Lewy body pathology – "Lewy body variant of AD" (38). It is further to be distinguished from a variety of disorders featured by extensive tau-pathology and NFT formation mainly in the cortex with variable involvement of subcortical structures but in the absence of sig-

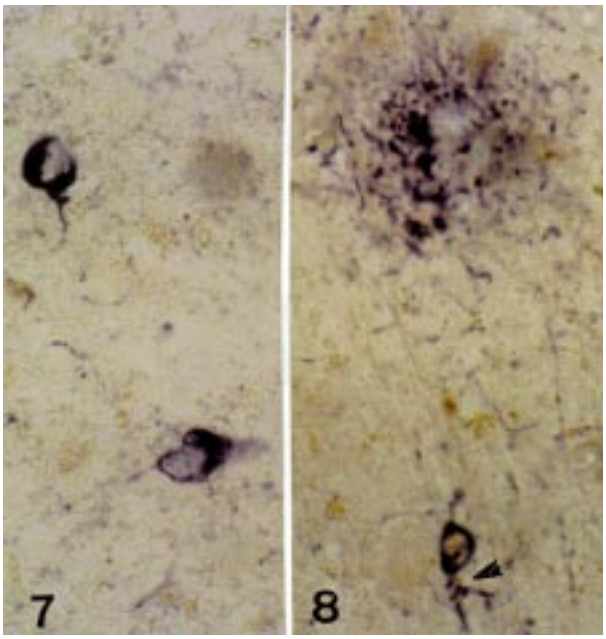


Figure 7. (left) Coiled bodies (tau-IR oligodendrocytes) in temporal white matter. AT-8 immunostaining x 500

Figure 8. (right) Coiled body (arrow head) and astrocytic plaque in frontal white matter of 99 year old female with MMSE 12/30. AT 8 immunostaining x 700

nificant amyloid (86, 96). The major such conditions to be excluded are the following:

1. Progressive supranuclear palsy, a Parkinson-like late onset disorder with axial rigidity, akinesia, postural instability, vertical eye movement inparment and frontal lobe symptoms (54) with same frequency of ApoE e4 as in healthy controls (75, 83), is morphologically characterized by widespread tau-positive NFTs and NTs in basal ganglia, many subcortical and brainstem nuclei including pontine base but except cerebellum, and tau-IR astroglial ("tufted astrocytes" and "astrocytic plaques"), and oligodendroglial inclusions ("coiled bodies") throughout the neuraxis (27, 28, 39, 54, 56). Cortical involvement in PSP considerably differs from that in AD, with highest density of tau pathology in prefrontal, angular, cingulate gyri to entorhinal, hippocampal and temporal cortices with sparing of association and occipital regions predominantly involved in AD; NFTs and NTs are mainly located in the deepest cortical layers in contrast to the bimodal pattern seen in AD, while entorhinal and hippocampal damage in both disorders are similar (7, 31, 41, 93). There are both biochemical differences in tau protein isoforms (PSP-NFT are composed of "doublet PHF") and the distribution of

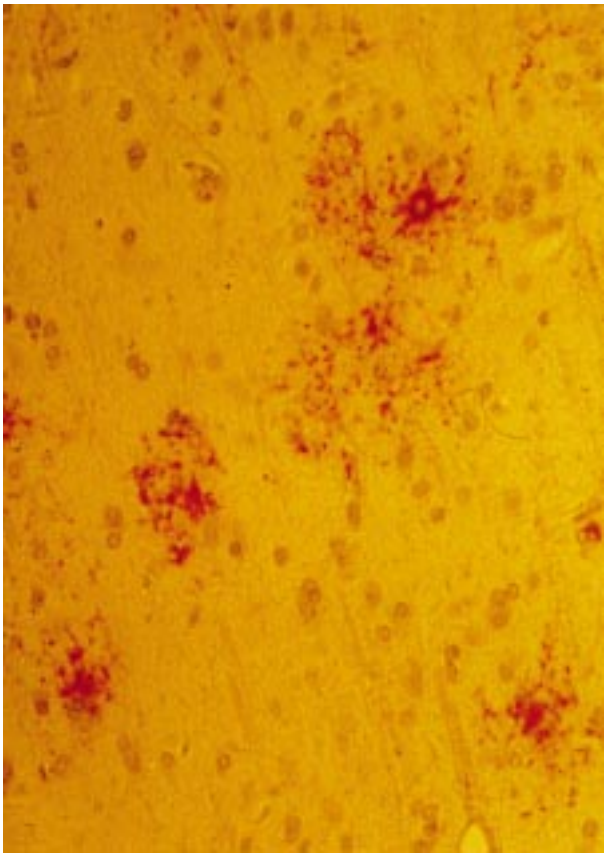


Figure 9. Tufted astrocytes and astrocytic plaques in white matter. AT 8 immunostaining x 250

cortical and subcortical lesions between PSP and both AD and NFT-SD (14, 42, 92, 93). With the recognition of overlaps in the clinical and pathological features of PSP and the variability of morphologic lesion patterns the preliminary NINCDS criteria for the pathological diagnosis of typical and atypical PSP (39) have been validated recently (54). However, atypical PSP cases (20) and superimposed AD (31) may cause difficulties in the distinction of PSP from both NFT-SD and "classical" AD with more extensive subcortical NFTs (56).

2. Autosomal dominant Dementia with neurofibrillary tangles linked to chromosome 17 (73, 78), is morphologically characterized by widespred tau pathology which may involve the hippocampus, pallidum, subthalamic nucleus, substantia nigra, pons, medulla, and other brainstem nuclei including the presence of neocortical tangles. The lesion pattern is morphologically similar to that of PSP and differs from both AD and NFT-SD, although both Aβ amyloid and neuritic plaques are totally absent. The ApoE e2/3 in one patient is similar to

	ApoE e2	ApoE e3	ApoE e4	p vs. NFT-SD
NFT-SD [2] (n=36)	0.11	0.86	0.03	
NFT-SD [46] (n=28)	0.39	0.50	0.11	<0.01
Controlsa (n=108)	0.037	0.852	0.111	n.s.
Controls (pooled)[a] (n=5008)	0.077	0.789	0.134	n.s.
Controls (octogen.)[a] (n=472)	0.09	0.82	0.09	n.s.
Controls (nonagen.)[a] (n=56)	0.071	0.893	0.036	n.s.
AD [2] (n=54)	0.00	0.65	0.35	<0.0005
AD (pooled)[a] (n=2896)	0.044	0.588	0.380	<0.0001
AD (octogen.)[a] (n=72)	0.01	0.75	0.24	<0.005
AD (nonagen.)[a] (n=60)	0.05	0.82	0.13	n.s.
AD (Braak stage IV)[a] (n=190)	0.095	0.705	0.200	<0.05
PSP [81] (n=12)	0.083	0.792	0.125	n.s.

[a] Data see (2); n.s.=not significant; n=number of alleles

Table 1. ApoE allele frequencies in NFT-SD, AD, PSP, and controls.

that reported in the Japanese cases of NFT-SD (73). For further details see Spillantini et al. in this symposium (p.000).

3. Diffuse neurofibrillary tangles with calcification (DWTC) (51): This slowly progressive dementia in presenile age (onset around age 50 yrs) mainly observed in females in Japan with duration from 3 to 24 (mean 9.9) years is clinically featured by aphasia, personality and behavioural disturbances, frequent parkinsonian signs, and final tetraplegia and apallic state. The brain shows localized symmetrical temporal or temporofrontal atrophy at CCT and autopsy with pallidal calcifications, and abundant NFTs widespread in the cerebral cortex accompanied by neuronal loss and astrogliosis, and few NFTs in some subcortical nuclei. Both cortical and subcortical NFTs show similar distribution as in AD, while senile plaques are absent.

4. Corticobasal degeneration, a rare sporadic late-onset disorder with rigid-akinetic syndrome, asymmetric limb apraxia, dystonia, action tremor and myoclonus, clinically resembling PSP or Pick's disease (87), is associated with lobar frontal or parietal atrophy, swollen achromatic tau- and ubiquitin-IR cortical neurons, NFT-like neuronal inclusions, widespread NTs and tau positive astrocytic plaques in gray and white matter (27, 28, 52, 69, 84); there may be occasional coexistent AD pathology (76). See also Bergeron et al in this symposium (Page 000)

5. Other diseases showing NFT/tau-related pathology with rare or absent Aβ deposits and neuritic plaques but having different clinical and morphological features include: Amyotrophic lateral sclerosis/Parkinson dementia complex of Guam (ALS/PDC) with NFTs identical to AD-NFT (14, 43, 71); postencephalitic parkinsonism (32, 94); dementia pugilistica (33), motor neuron disease with NFTs (42), Gerstmann-Sträussler-Scheinker disease with tangles (35), adult onset Hallervorden-Spatz disease (25), Niemann-Pick disease type C (55), subacute sclerosing panencephalitis (5, 58, 61), and argyrophillic grain dementia (9, 11, 89, 90) that has been observed to coexist in 20 to 66% of NFT-SD (91; personal observations). NFT-SD is morphologically distinct from frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) that is clinically featured by personality change and progressive dementia but shows no Alzheimer-related lesions (1, 30), as well as from multiple system tauopathy (35).

Conclusion

In conclusion, NFT-SD is a sporadic form of very late onset dementia mainly of the “limbic” Alzheimer type with no or very little subcortical neurofibrillary pathology, and is distinct from other tauopathies, including PSP, in which amyloid deposition is rare in the absence of ApoE e4 or due to a protective effect of predominant ApoE e3 or 2 alleles. Although genetically distinct from “classical” AD featured by both cortical plaques and tangles, NFT-SD may represent a variant of AD or of pathologic aging occurring in very late age, but its nosological position within the genotypical and phenotypical heterogenous AD-“syndrome” remains to be elucidated.

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