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Different variants of frontotemporal dementia: a neuropathological and immunohistochemical study

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Abstract Histological and immunohistochemical findings in 20 cases of frontotemporal dementias – 8 cases of dementia of frontal lobe type (DFT), 7 cases of Pick's disease (PD), and 5 cases of motor neuron disease with dementia (MND/D) – are presented. Common features of all three syndromes were: frontotemporal atrophy, involvement of subcortical nuclei, and swollen chromatolytic cells. Ubiquitin (Ub)-positive and tau-negative inclusions in cortical, hippocampal, and motor neurons were found in MND/D and DFT cases, suggesting a common pathogenesis of MND/D and DFT. MND/D showed the same cytoskeletal alterations in motor nuclei as MND without dementia: Bunina bodies and skein-like, Ub-positive inclusions. DFT differed from PD in the preponderance of histopathological changes in upper cortical layers, the sparseness of chromatolytic cells, and the absence of tau-positive Pick bodies (PBs). There were, however, two transitional cases showing Pick-type histology but no PBs, thus linking DFT and PD. PBs expressed chromogranin B and secretoneurin strongly, but chromogranin A only weakly. They were negative for the 70-kDa heat-shock protein, metallothionein, and glutathione-S-transferase.

Dedicated to Prof. F. Gullotta on the occasion of his 65th birthday

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Key words Frontotemporal dementia · Dementia of frontal lobe type · Pick's disease · Motor neuron disease with dementia · Pick bodies

Introduction

Dementia of Alzheimer type (DAT) is thought to be the most frequent cause of progressive dementing syndromes in the elderly [29]. Recently, however, it has become increasingly recognized that certain non-Alzheimer forms of cerebral atrophy are relatively common. Two types of histology underlie the atrophy that share an identical distribution in frontal and anterior temporal lobes. The most common type is characterized by neuronal loss, microvacuolation, and mild gliosis, especially in upper cortical layers of affected regions. The second form corresponds to the typical Pick-type histology, consisting of intense neuronal depletion and astrocytosis in all cortical layers, inflated cells, and argyrophilic inclusions (Pick bodies, PBs). Clinically, signs of frontotemporal lobe dysfunction with insidious onset progress slowly [11, 21, 43].

These conditions have been reported as "dementia lacking distinctive histopathology" [34, 35], "frontal lobe dementia" or "dementia of frontal lobe type (DFT)" [9, 20, 42, 43, 48]. Rare conditions such as motor neuron disease with dementia (MND/D) or progressive aphasia also belong to this group [49, 55].

To date, there is no universally accepted morphological definition of Pick's disease (PD). Some authors accept circumscribed lobar atrophy without characteristic histology [24, 57], for others ballooning of neurons is obligatory [38]. Since the syndrome of frontotemporal degeneration is heterogeneous [10] and ballooned neurons occur in a variety of neurodegenerative conditions [30, 39], it has been proposed that only the combination of progressive dementia, lobar atrophy and neuronal argyrophilic inclusions is diagnostic of PD [50].

To define the relationship between these conditions, we performed an extensive neuropathological and immunohistochemical study of 20 cases with DFT, PD, and MND/D.

Materials and methods (Tables 1, 2)

Eight cases of DFT defined by frontotemporal atrophy and absence of tau-positive inclusions in four males and four females were examined. The disease started between 37 and 66 years of age with a duration of 19–72 months. A positive family history was present in two cases. All patients developed behavioral changes followed by amnesia and global cognitive decline. Aphasia, spastic paresis, and terminal parkinsonian features were each present in one case.

Seven cases were classified as PD because of frontotemporal lobar atrophy, numerous chromatolytic cells and argyrophilic tau-positive inclusions. The age at onset in the four males and three females varied from 48 to 65 years; the disease lasted between 1 and 14 years. All patients suffered from early behavioral changes, with amnesia and dementia evolving later during the course of the disease. A positive family history was reported in one case.

Five cases of MND/D (two male, three female) had clinical and morphological evidence of MND. All showed signs of bulbar palsy, while four had upper and lower motor neuron signs. In two

Table 1 Neuropathology of frontotemporal dementias. Cases 1–8: dementia of frontal lobe type; cases 9–15: Pick's disease; cases 16–20: MND/dementia (*MND* motor neuron disease, *Macro* macroscopic atrophy, ( ) slight or moderate atrophy, =/> predominance of atrophy, *r/l* left- or right-sided predominance, *FC* frontal cortex, *NCL* nerve cell loss, *SP* spongiosis or microvacuolation, *G* gliosis, *UL* second and third cortical layer, *ULL* second, third and sixth cortical layer, *ML* third and fifth cortical layer, *AL* all cortical layers, *B* orbitofrontal predominance, *TC* temporal cortex, *MC* motor cortex, *PC* parietal cortex, *ins* insula, *GC* anterior cingulate cortex, *AM* amygdaloid nucleus, *L* lateral, *B* basolateral, *AN* all nuclei, *HC* hippocampus, *C1+2* sectors of hippocampus, *S* subiculum, *Gp* gyrus parahippocampalis, *ST* striatum, *NC* caudate nucleus only, *P* globus pallidus, *TH* thalamic nuclei, *DM* dorsomedial nuclei, *VA* ventral anterior nuclei, *Sn* substantia nigra, $_{c,\,r}$ pars compacta, pars reticularis, *v,d,i* ventrolateral, dorsal, intermediate cell group according to [19], *MN* motor nuclei of brain stem and spinal cord, *Con/Mann* classification of Constantinides et al./Mann et al. [13, 43], [1] additional Fahr's syndrome, –/+/++/+++ no slight moderate, or severe affection)

	Macro	FC			TC			Other regions											Con/ Mann
		NCL	SP	G	NCL	SP	G	MC	PC	INS	GC	AM	HC	ST	P	TH	Sn_c	MN	
1	(FC),Sn	+ UL	++ UL	+ ULL	–	–	–	–	+	–	–	–	++ C1-S	–	–	–	++ vid	–	B/C
2	–	+ UL	++ UL	–	–	–	–	–	–	–	–	–	–	–	–	–	+ v	–	B/A
3	TC_l	–	–	–	++ UL	++ UL	++ ULL	–	–	++	–	++ LB	+ S-Gp	–	–	–	–	–	C1/A
4	TC_l	–	–	–	++ UL	++ UL	++ UL	–	–	–	–	++ AN	+ C1-S	–	–	–	–	–	C1/A
5	TC_r	–	–	–	++ ML	++ UL	++ UL	–	–	+	–	++ LB	+ S-Gp	–	–	–	–	–	C1/A
6	FC = TC Sn	$++_B$ ML	++ UL	++ ULL	++ ML	++ UL	++ ULL	–	–	++	+	+ LB	+ S-Gp	++	–	–	$++_r$ vd	–	B/C
7	FC = TC, ST,Sn	$++_B$ ML	+ UL	++ AL	++ ML	+ UL	++ AL	+	–	++	++	++ AN	++ C2-S	++ NC		–	–	–	C2/C
8	$FC_l = TC_l$	$+++_B$ AL	+ AL	+++ AL	+++ AL	+ AL	+++ AL	–	–	++	–	+++ AN	++ C1-S	++	–	++ DM	$++_r$ vdi	–	C2/C
9	$TC > FC_r$	+ ML	+ ML	–	+++ ML	+ ML	+++ AL	–	–	++	+	+ AN	–	–	–	–	–	–	A/B
10	TC = FC	+++ AL	++ AL	+++ AL	+++ AL	++ AL	+++ AL	++	+	++	+	++ AN	+ C2-S	–	–	–	–	–	A/B
11	FC = TC, AM	$+++_B$ AL	++ AL	+++ AL	+++ AL	+ AL	+++ AL	+	+	+	+	+++ AN	–	++	+	++ DM	–	–	A/B
12	TC = FC Sn	$+++_B$ AL	++ AL	+++ AL	+++ AL	+ AL	+++ AL	++	++	+	+	++ LB	++ C2-3	–	–	DM	+ v		A/B
13	$FC > TC_r$	$+++_B$ AL	+ AL	++ AL	++ AL	+ AL	++ AL	+	+				+ C1-Gp	–	+1	–	–	–	A/B
14	$TC > FC_r$				+++ AL	+ AL	+ AL	–	–	++		++ AN	+ C2-Gp	–	–				A/B
15	FC,INS	++ AL	–	++ AL	+ ML	–	+ ML	–	–	++	+	–	+ C2-3	+ NC	–	DM VA	$+_r$ v	–	A/B
16	(FC),Sn	+ UL	++ UL	+ ULL	–	–	–	+	–	–	–	–	–	–	–	–	++ vd	+++	–/D
17	(FC)	+ UL	++ UL	+ ULL	+ UL	++ UL	+ ULL	+	–	–	–	–	–	–	–	–	+	+++	–/D
18	–	+ UL	++ UL	+ ULL	–	–	–	–	–	–	–	–	–	–	–	DM	+ v	+++	–/D
19	TC				+ UL	+++ UL	++ ULL							–	–	–	–	+++	–/D
20	(FC)	+	++ UL	+ UL	+	++ UL	+ UL	–	–			–	–	–	–	–	+ v	++	–/D

Table 2 Distribution of ubiquitin- and tau-positive inclusions in frontotemporal dementias. (*U* ubiquitin-positive intraneuronal inclusions, *t* tau-positive intraneuronal inclusions, *BS* brain stem, *NFT/ß-Am* neurofibrillary tangles/diffuse β-protein positive plaques, *N* neurofibrillary tangles, *Lb* Lewy bodies in substantia nigra, *Pc* swollen Pick cells, *F* skein-like or hyaline argyrophilic inclusions, *Bb* Bunina bodies, [1] substantia nigra, [2] posterior horn, [3] nucleus basalis of Meynert, [4] neuropil threads, argyrophilic grains, and glial inclusions in basal ganglia, thalamus, brain stem, lower cortical laminae and subcortical white matter, – negative immunoreactivity, +/++/+++ slight, moderate, or high density; for other abbreviations see Table 1)

	FC U/t	TC U/t	MC U/t	PC U/t	INS U/t	GC U/t	AM U/t	HC U/t	ST U/t	TH U/t	BS U/t	MN U/t	NFT/ β-Am
1	– Pc	– Pc	–	–	–	–	– N	– N,Pc	– Pc	–	– Pc[1]	–	+/++
2	+/– Pc	+/– Pc	+/–	+/– Pc	–	– Pc	+/– Pc,N	+/– N	–	+/–	–	+/– F	+/+
3	–	+/–	–	–	–	–	+/– N	+/– N	–	–	–	–	+/++
4	+/–	+/–	–	–	–	–	–	+/–	–	–	–	–	–/–
5	+/–	+/–	–	–	–	+/–	–	+/– N	–	–	–	–	+/–
6	–	–	+/–	–	–	–	–	+/– Pc	–	–	–	+/– F	–/+
7	–	–	–	–	–	–	–	+/–	–	–	– N	+/– F	+/–
8	–	–	–	–	–	–	–	–	–	–	+/–[1] Lb	+/– F	–/–
9	+/+	+/++ Pc	–	+/+	– Pc	– Pc	+/++ Pc	+/+++ Pc	–	–	+/+	–/+[2]	–/–
10	+/++ Pc	+/+++ Pc	–	–	–	–	+/++ Pc	+/+++ Pc	–	–	+/++ Pc		–/–
11	+/+++ Pc	+/++ Pc	+/++	–/+	–	–	+/+ Pc,N	+/+ Pc,N	+/–	–	+/+	–	++/+
12	– Pc	– Pc	– Pc	–	–	– Pc	–	+/+	–	–	– Pc		–/–
13	+/++ Pc	+/++ Pc	–	–				+/+++ Pc	+/+[3]	+/+	+/+		–/+
14		+/++ Pc			+/– Pc		+/+++ Pc	+/+++ Pc	+/+			–	–/–
15	+/++ Pc	+/+ Pc	–	+/+	–	–	+/++	+/+	+/++ N	– N	+/+ N	–	+/–[4]
16	–	–	–	–	–	–	–	+/– N	+/–	–	–	+/– F,Bb	+/+
17	– Pc	–	+/–	–	–	–	–	–	–	–	–/– N,Lb[1]	+/– F,Bb	+/+
18	–	–	–	–	–	–	– N	– N	–	–	– N	+/– F,Bb	+/+
19		+/– N							–	–	–	+/– F,Bb	–/–
20	–	–		–			–	– N	–	–	–	+/– F,Bb	+/–

cases, personality changes preceded motor symptoms by 6 and 12 months, respectively; in the other three cases these symptoms manifested simultaneously. Parkinsonian features were present in one case. The age at onset ranged from 50 to 69 years and disease duration from 7 to 36 months. DAT was excluded according to different criteria [44, 56]; features of DAT pathology were categorized according to recently published criteria [6].

The brains, obtained at autopsy with a postmortem delay of 5–48 h, were fixed in 7% formalin solution for at least 2 weeks. After gross examination, tissue blocks were taken from superior frontal, orbitofrontal, temporopolar, anterior cingulate, motor, superior parietal and occipital cortices, amygdala, hippocampus, nucleus basalis of Meynert, striatum, thalamus, midbrain at the level of the third and fourth nerve nuclei, pons with trigeminal motor nucleus, medulla with hypoglossal nucleus and spinal cord. For routine neuropathological evaluation, 10-µm-thick sections were stained with hematoxylin-eosin, cresyl-violet, Klüver-Barrera, and Gallyas and Campbell stains and by Bodian silver impregnation. To evaluate the precise topographic distribution of histopathology, large hemispheric sections from 14 cases were examined.

Immunohistochemical investigations were performed on 4-µm-thick serial sections from all these regions using the following monoclonal (M) or polyclonal (P) primary antibodies: anti-ubiquitin (Ub) (P, Dako, Glostrup, Denmark, 1:800), anti-tau (P, Dako, 1:200), anti-β-protein (M, Dako, 1:200), anti-glial fibrillary acidic protein (GFAP) (P, Dako, 1:400), anti-neurofilament protein 68 (M, Dako, 1:200), anti-PGP9.5 (P, Ultraclone Ltd., UK, 1:800). Selected areas – usually frontal cortex and hippocampus – were stained with additional primary antibodies against the 70-kDa heat-shock protein (HSP70) (P, Dako, 1:1000), chromogranin A

(M, Biogenex, San Ramon, 1:800; M, Dako, 1:100), secretoneurin (P, 1:2000; [32, 54]), glutathione-S-transferase (GST) (P, Biogenex, Mainz, Germany, 1:200), and metallothionein (M, 1:20 000, [53]). For chromogranin B antiserum (P, 1:2000), a peptide (PE-11) corresponding to amino acids 555–565 of the primary amino acid sequence of human chromogranin B [4] was synthesized by standard *t*-BOC chemistry and purified by reverse-phase high-performance liquid chromatography. The peptide structure was verified by mass spectrometry and Edman degradation. PE-11 indicates the first (proline) and last amino acid (glutamic acid) of the peptide plus the total number of amino acids. The peptide was coupled to maleimide-activated keyhole limpet hemocyanin via an extra N-terminal cysteine residue. This conjugate was used to generate an antiserum in Chinchilla Bastard rabbits according to a standard immunization protocol. Sections from frontal and temporal cortex and from cerebellum were examined for prion protein (PrP) accumulation. For this, tissue pretreatment included immersion of sections in formic acid followed by hydrolytic autoclaving as described previously [33]. The antibody used was MMWB 138P (Gö-138P), a mouse monoclonal antibody raised against a synthetic peptide (codons 138–152) of human PrP. Creutzfeldt-Jacob disease cases with or without kuru plaques were used as controls. Avidin-biotin-peroxidase complex (ABC) and alkaline phosphatase-antialkaline phosphatase (APAAP) methods with diaminobenzidine and neufuchsin as chromogen were performed as described elsewhere [5].

Results

Neuropathological features of DFT (cases 1–8)

Gross examination showed moderate, sometimes asymmetrical, frontal (one case), temporal (three cases), or frontotemporal atrophy (three cases). Case 2 was grossly normal. There was depigmentation of the substantia nigra in three cases and shrinkage of the striatum in one.

Histologically, the frontotemporal cortex of all cases showed nerve cell loss, spongiosis and gliosis, albeit of widely varying degree and distribution. Spongiosis was the most conspicuous finding and was most commonly found in the second and third cortical layers; neuronal loss occurred at the same location, while in four cases the deeper cortical layers were also affected. In five cases astrocytic gliosis was seen in the first to third and sixth cortical layers, but in two cases the whole cortical ribbon was involved (Table 1). Atrophy affected the frontal cortex in two, the temporal cortex in three, and both regions in three cases. In three cases the degeneration predominated in orbitofrontal regions. Temporal atrophy particularly involved anterior parts of the lobe and gradually decreased posteriorly. The superior temporal gyrus was only minimally affected in all cases. All nuclei of the amygdala (three cases) or only the basolateral and lateral nuclei (three cases) showed severe nerve cell loss. Hippocampal atrophy extended from the C1 sector to the subiculum (three cases), from the C2 sector to the subiculum (one case), or from the subiculum to the parahippocampal gyrus (three cases). Additional cortical and subcortical sites of degeneration are listed in Table 1. Lewy bodies were seen only in case 8. α-Motor nuclei of brain stem and spinal cord were normal and Bunina bodies were absent in all cases. Occasional chromatolytic cells were detected in pyramidal cells of the frontotemporal cortex or the hippocampus (Fig. 1A, Table 2).

Immunohistochemically, all cases showed many dot-like Ub-positive deposits in the neuropil of frontotemporal cortex, six also having intracytoplasmic Ub-positive and tau-negative round inclusions in frontotemporal and hippocampal pyramidal cells. These deposits did not react with any of the other antibodies (Fig. 2). Four cases showed Ub-positive filamentous deposits in motor nuclei of brain stem and spinal cord. Bunina bodies were consistently absent (Fig. 1B, Table 2).

Neuropathological features of PD (cases 9–15)

Macroscopically, all cases showed severe, sometimes asymmetrical (three cases), knifeblade atrophy of the

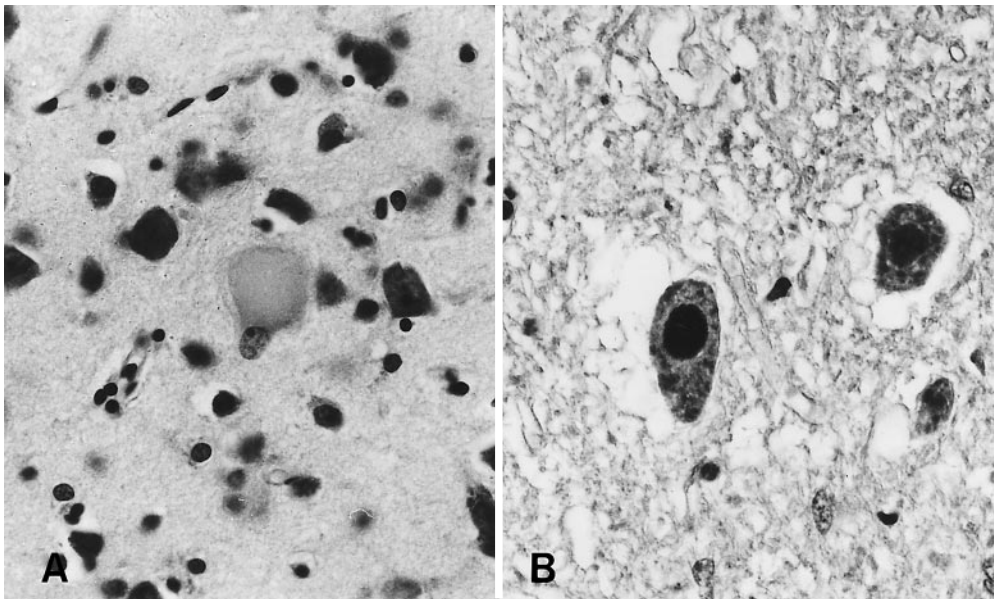

Fig. 1 Swollen chromatolytic cell in frontal cortex (**A**) and ubiquitin (Ub)-positive hyaline inclusion in α-motor neuron of spinal cord (**B**) in a case of dementia of frontal lobe type (DFT). **A** Case 2, Nissl; **B** case 6, anti-Ub, avidin-biotin-peroxidase complex method (ABC); **A**, **B** × 500

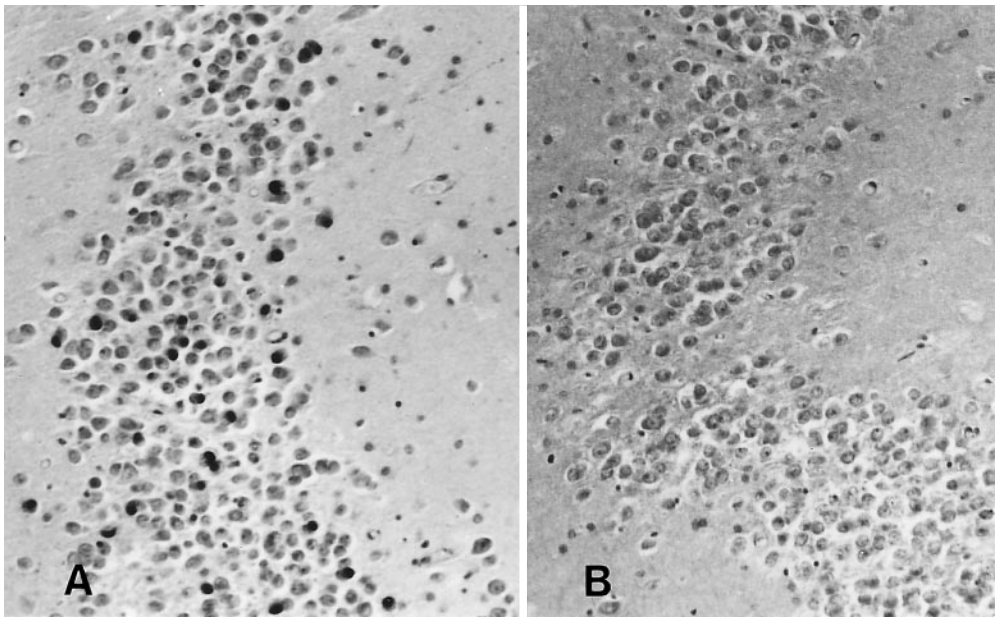

Fig. 2 Ub-positive (**A**), tau-negative inclusions (**B**) in granule cells of the hippocampus in a DFT case. **A** Anti-Ub, **B**: anti-tau, ABC; **A**, **B** case 4, × 100

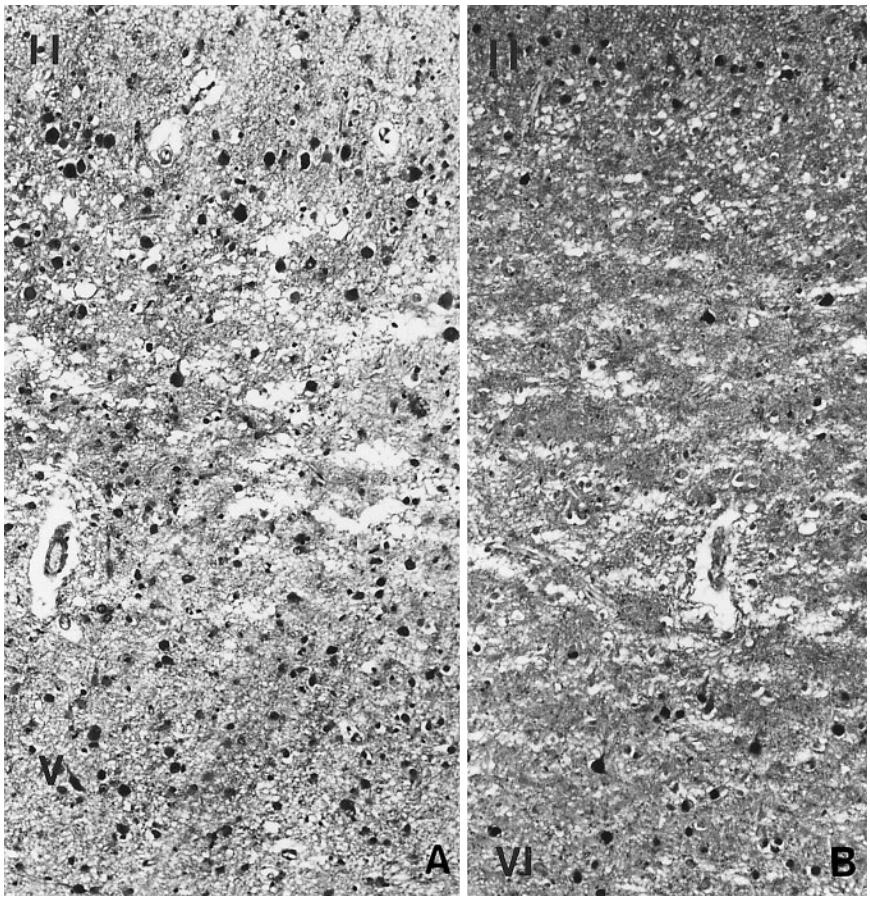

Fig. 3 Swollen Pick cells detected by a positive reaction with PGP9.5 (**A**) are seen in all cortical layers with a preponderance in the third and fifth layers; tau-positive inclusions (**B**) are present especially in second and sixth cortical layers. **A** PGP9.5, ABC; **B** anti-tau, ABC; **A**, **B** case 10, × 120

frontotemporal cortex with temporal predominance in two and frontal predominance in one case. In one case the substantia nigra and in another case the amygdala were significantly degenerated.

Histologically, marked nerve cell loss, spongiosis and gliosis were detected in the frontotemporal cortex of all cases; the temporal cortex was the preferred site in two cases and the frontal cortex in two cases. Neuronal loss and gliosis were more severe than in DFT cases and all cortical layers were evenly affected in maximally involved regions, whereas in less-affected areas cell loss was confined to the third and fifth cortical layers (Table 1). Atro-

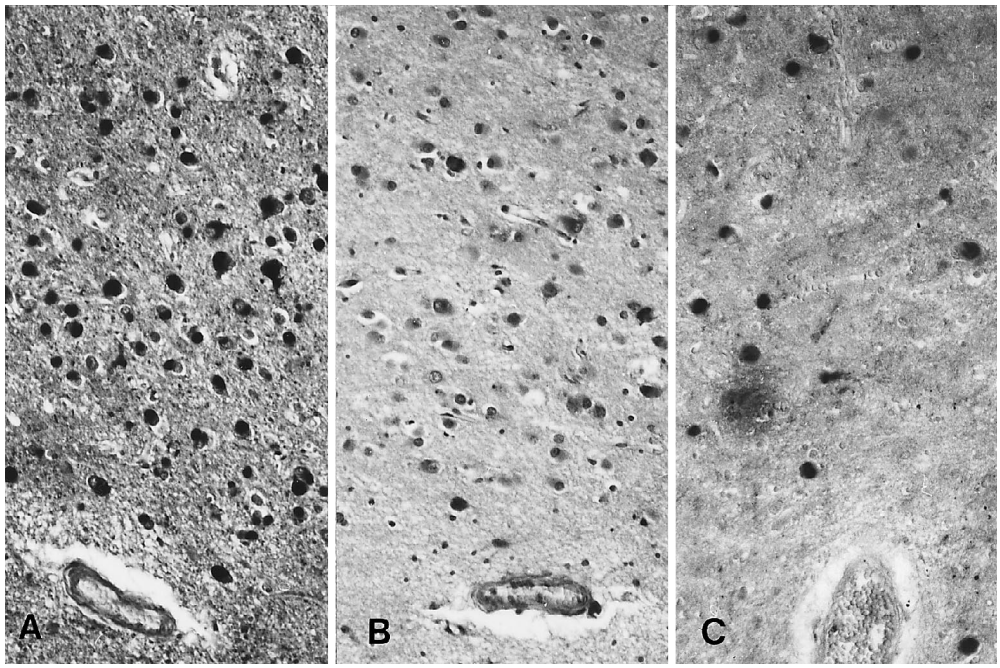

Fig. 4 Many Pick bodies are strongly positive for anti-tau (**A**) but show a weaker immunopositivity for Ub (**B**) and anti-chromogranin B (**C**) as demonstrated in granule cells of the fascia dentata. **A** Anti-tau, ABC; **B** anti-Ub, ABC; **C** anti-chromogranin B, alkaline phosphatase-anti-alkaline phosphatase; **A**–**C** case 14, × 200

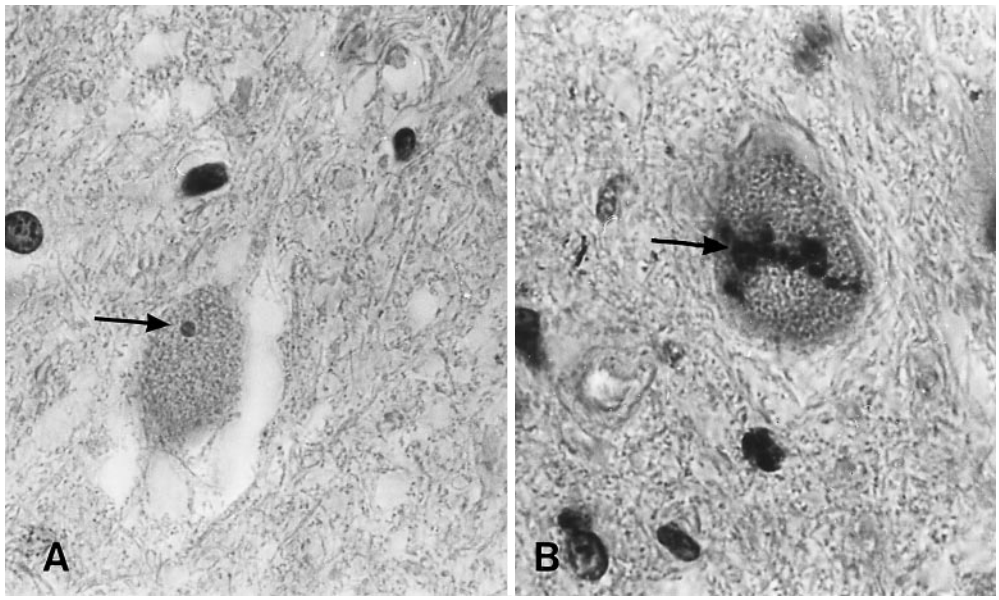

Fig. 5 In motor neuron disease with dementia, Bunina bodies (**A**, *arrow*) and skein-like filaments (**B**, *arrow*) were detected in motor nuclei of brain stem and spinal cord. **A** H&E, **B** anti-Ub; **A**, **B** case 19, × 520

phy of the whole frontal lobe was seen in four cases, whereas three cases showed predominantly orbitofrontal atrophy. In the temporal lobe, histopathological changes gradually decreased posteriorly and the first temporal gyrus was generally unaffected. Additional sites of degeneration are given in Table 1. In four cases, the whole amygdala was homogeneously affected, whereas in one case atrophy was confined to the lateral and basolateral nuclei. Nerve cell loss and gliosis were found in the hippocampus of five cases, especially in the C2 sector. Ballooned nerve cells (Pick cells, PCs), present in all cases, usually predominated in the third and fifth cortical layer. They were found in various cortical areas, in two cases even in many nuclei of the brain stem. PCs showed a strong reaction with anti-PGP9.5, with anti-neurofilament and some times with anti-tau (Fig. 3A).

PBs could be detected in all cases in differing amounts and with varying distribution (Table 2). The highest density of PBs was seen in the hippocampal fascia dentata in four and in the frontal cortex in two cases. In the frontotemporal cortex, they predominated in lamina II and VI; other laminae were less affected (Fig. 3B). PBs were also seen in different nuclei of the brain stem (five cases) and in spinal nuclei of the posterior horn (one case). Anti-tau immunostains showed the highest sensitivity for PBs, followed by anti-chromogranin B, and, with the lowest sensitivity, anti-Ub, anti-secretoneurin, and Bodian silver stain (Fig. 4). Chromogranin A was only expressed in oc-

casional PBs. Metallothionein and GST were not found in either PCs or PBs; PCs in the hippocampus of case 9 showed a weak HSP70 immunoreaction.

Neuropathological features of MND/D (cases 16–20)

Macroscopically, only slight atrophy of frontal (three cases) or temporal lobes (one case) was remarkable. The substantia nigra was significantly depigmented in one case.

Histologically, slight spongiosis, nerve cell loss, and gliosis were seen in the frontotemporal cortex. Nerve cell loss was often difficult to detect and spongiosis predominated in the second and third cortical laminae. Gliosis was found in the first to third and sixth layers. The frontal cortex or the anterior temporal cortex was involved in four or three cases, respectively (Table 1). Although only one patient had extrapyramidal signs, cell loss and gliosis of the substantia nigra were observed in four cases, while only one of them had Lewy bodies (Table 1). Case 18 showed nerve cell loss and gliosis of both dorsomedial thalamic nuclei. In all cases the most significant cell loss, however, was seen in α-motor nuclei of brain stem and spinal cord. The motor cortex was affected in two and the pyramidal tracts in four cases. The motor nuclei of brain stem and spinal cord harbored Bunina bodies and Ub-positive skein-like filaments in all cases (Fig. 5A, B). Abundant dot-like Ub-positive deposits were present in the cortical neuropil; in cases 16 and 17 some neurons in frontotemporal cortex and hippocampus showed intracytoplasmic Ub-positive and tau-negative inclusions, which did not react with any of the other antibodies (Table 2).

Altogether, 11 of 20 cases showed occasional neurofibrillary tangles (NFTs) in limbic areas or brain stem nuclei, mature neuritic plaques were always absent and in 9 cases, diffuse β-protein-positive plaques were seen in upper cortical layers of the frontotemporal cortex. Case 15 had numerous tangles, neuropil threads, argyrophilic granules and tau-positive argyrophilic glial inclusions in the basal ganglia, thalamic nuclei and brain stem. Metallothionein and GST were strongly expressed in fibrillar astrocytes, but not in any of the described inclusions. None of the cases was immunoreactive to PrP antibodies.

Discussion

Recent publications have aroused increasing interest in certain non-Alzheimer dementias without distinctive histopathological features, referred to as dementia lacking distinctive histopathology [18, 34, 35], dementia of frontal lobe type (DFT) or frontal lobe dementia [9, 10, 42, 43, 48, 50], and related syndromes such as MND/D [49] or progressive aphasia [55]. DFT accounts for 3–20% of dementing syndromes [18]. The slowly progressive disorder (mean duration 7.5 years, range 3–17 years) is characterized by personality changes, stereotyped behavior, and language impairment. Intra vitam differentiation between PD and DFT is rarely possible [21]. In contrast to DAT, memory, spatial orientation, praxis and gnosia are initially relatively unaffected; later on a general decline in higher cortical functions is present [21, 35]. A positive family history is observed in about 50% of DFT cases [43]. Neuropathological features consist of moderate to severe, usually symmetrical, atrophy confined to the frontal and temporopolar regions with widening of the ventricles. Asymmetrical atrophy is generally seen in patients with progressive aphasia [35, 50]. According to recently published criteria for DFT, loss of pyramidal cells is severe in the second and third and only mild in fifth cortical layers. Spongiform degeneration of the second and third layers is combined with moderate to severe astrocytic gliosis of gray and white matter, occasionally predominating in the first to third and sixth layers [10, 43]. These lesions frequently spread to the insula and cingulate gyrus, while the posterior temporal, parietal, and occipital cortices are usually spared.

The morphological features of DFT in the present study were generally in line with previous reports, although asymmetry, which is said to be a typical feature of PD, was seen in 50% of DFT cases. Atrophy was highly variable and spared the frontal lobe in three cases, as also reported in a previous study [18]. Whether there was a frontal or temporal predominance of atrophy did not influence the neurobehavioral symptoms (see also [17]). Spongiosis and cell loss predominated in the upper cortical layers, but in four cases the third and fifth layers were severely involved. Two cases showed Pick-type histology without inclusions and ballooned cells. Together with similar reports [10, 43], these cases show that DFT may belong to the PD spectrum. Although limbic structures and subcortical nuclei are usually spared, several authors have reported a significant degeneration of these nuclei [34, 43, 50, 58, 62]. These areas, typically severely involved in PD, were also markedly affected in all but one of our cases. Cell loss was pronounced in the C1 sector and subiculum of the hippocampus, and predominated in lateral and basolateral nuclei of the amygdala. Ballooned cells occurred only sporadically, as has been shown before [8, 14, 43]. The occurrence of extramotor (six cases) and motor (four cases) Ub-positive inclusions, a hallmark of MND [5, 63], in DFT cases without clinical or further morphological evidence of MND (such as loss of motor neurons and Bunina bodies) is in line with two recent studies [14, 27] and suggests a pathogenetic link between DFT and MND/D.

PD is a rare disorder, accounting for 0.4–2% of all dementing syndromes [29], and manifests itself mostly in the fifth and sixth decades with signs of frontal lobe dysfunction [18, 21, 57]. Neuropathologically, it is characterized by a severe frontotemporal lobar atrophy with neuronal loss and gliosis, chromatolytic neurons (PCs), and argyrophilic inclusions (PBs). As in DFT, atrophy usually predominates in the polar regions of frontotemporal lobes, decreasing posteriorly [3, 7, 13, 28, 36, 41]. In these regions, cell loss preferentially affects the supragranular layers [28, 57]. Cingulate gyrus, insula, hippocampal formation, and

amygdala are usually severely involved [3, 43]. Various subcortical structures, such as basal ganglia, nucleus basalis of Meynert, substantia nigra, locus coeruleus, and central gray are also affected, particularly in the generalized variant of PD [1, 36, 46, 59, 60, 66]. Massive gliosis of the centrum semiovale and severe degeneration of the fronto- and temporopontine tracts are common [8].

PBs are spherical argyrophilic inclusions consisting of randomly distributed straight fibrils (10–20 nm wide) intermingled with larger constricted fibrils (15–30 nm wide) with a periodicity between constrictions of about 160 nm [7, 23, 46, 47]. In the cerebral cortex, they predominate in the granule cell layer of the dentate gyrus and the pyramidal cells of Ammon's horn, subiculum, entorhinal cortex, and the second and sixth layers of frontotemporal cortex [23]. However, involvement of subcortical structures is common [66]. Immunohistochemically, PBs resemble NFTs in some respects. They are associated with phosphorylated neurofilament epitopes, microtubule-associated protein tau and Ub [40, 52, 61].

The present study confirms most of these findings. PBs were widespread and distributed in different subcortical and brain stem nuclei; in one case they were even detected in the spinal cord. In contrast to previous reports, only few PBs expressed chromogranin A, which also occurs in NFTs [66]. However, they expressed chromogranin B and secretoneurin, which has, to our knowledge, not been reported so far. HSP70, another heat-shock protein that can be detected in NFTs [22], was absent from PBs.

Whereas minor cognitive changes are not infrequent in patients with MND/amyotrophic lateral sclerosis (ALS), only 3% of sporadic and 7–15% of familial MND/ALS patients suffer from frank dementia. MND/D starts mostly in the sixth decade with a male to female ratio of 2:1 [26]. Neuromuscular symptoms dominate the clinical course. Dementia is of the frontal lobe type [49], but signs of temporal lobe impairment, such as Klüver-Bucy syndrome [16] and psychotic symptoms, also occur [25, 63]. Extrapyramidal symptoms sometimes appear during the later stages [45].

The present study shows that loss of α-motor neurons and cytoskeletal abnormalities in MND/D do not differ from those in MND/ALS patients without dementia. Neurons usually contain Bunina bodies and skein-like filaments, and spheroids are formed at the proximal axons [5, 37]. These findings suggest that MND/D belongs pathogenetically to MND/ALS. Although the pyramidal tract was often unaffected in a large study [45], it was degenerated in all but one of our cases. In MND/D, the frontotemporal cortex displays spongiosis, gliosis and nerve cell loss in the upper cortical layers. Subcortical regions such as the striatum, globus pallidus, thalamus, subthalamic nucleus, red nucleus, dentate nucleus, and hypothalamus are also affected [26]. One case in the present study showed neuronal loss in the dorsomedial and centromedian thalamic nuclei, thus resembling thalamic dementia [15]. The pars compacta of the substantia nigra, affected in four of our cases, has been described as degenerated in 54% of MND/D cases, although severe extrapyramidal symptoms are exceptional [45]. As our study shows, limbic structures such as the basolateral nuclei of the amygdala, nucleus accumbens, and subiculum are only sometimes involved [16, 31]. Ub-positive intraneuronal inclusions occurring in the frontotemporal cortex and granule cells of the dentate fascia are a frequent but irregular finding in MND/D brains [51, 63].

Except for a few case reports of combined DAT and PD, the classic neuropathological features of DAT are typically absent from DFT, PD and MND/D brains. Eleven cases in our study showed a very early, limbic stage of DAT pathology [6], which suggests a possible relationship between DAT and PD [23].

Case 15 is somewhat atypical in showing concomitant neuropathological features of PD (frontotemporal atrophy, PCs, and PBs) and progressive supranuclear palsy (threads, tangles, and argyrophilic glial inclusions), a combination which has been reported previously [2].

Although spongiform changes in the frontotemporal cortex are superficially reminiscent of prion diseases, and PrP immunohistochemistry can be of value in the differential diagnosis of frontotemporal dementias, there is no etiological connection with this disease group [12, 34].

In conclusion, our study demonstrates that DFT, PD, and MND/D share many histological features, thus supporting the concept that they are mere variants of frontotemporal atrophy [11]. This is also stressed by the demonstration of motor and extramotor Ub-positive inclusions in both DFT and MND/D. Because MND/D shows the same cytoskeletal abnormalities as MND, it really belongs to the spectrum of MND. DFT differs from PD by the preponderance of histopathology in upper cortical layers, the sparseness of chromatolytic cells and the absence of tau-positive, argyrophilic inclusions. These inclusions show strong chromogranin B and secretoneurin and weak chromogranin A immunoreactivity, but are negative for HSP70, metallothionein and GST. Frontotemporal dementias do not belong to the prion diseases since they do not display PrP immunopositivity.

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References

1. Arima K, Akashi T (1990) Involvement of the locus coeruleus in Pick's disease with or without Pick body formation. Acta Neuropathol 79: 629–633
2. Arima K, Murayama S, Oyanagi S, Akashi T, Inose T (1992) Presenile dementia with progressive supranuclear palsy tangles and Pick bodies: an unusual degenerative disorder involving the cerebral cortex, cerebral nuclei and brain stem nuclei. Acta Neuropathol 84: 128–132
3. Ball MJ (1979) Topography of Pick inclusion bodies in hippocampi of demented patients. A quantitative study. J Neuropathol Exp Neurol 38: 614–620

4. Benendum UM, Lamouroux A, Konecki DS, Rosa P, Hille A, Baeuerle PA, Frank R, Lottspeich F, Mallet J, Huttner WB (1987) The primary structure of human secretogranin I (chromogranin B): comparison with chromogranin A reveals homologous terminal domains and a large intervening variable region. EMBO J 6: 1203–1211
5. Bergmann M (1993) Motor neuron disease/amyotrophic lateral sclerosis- lessons from ubiquitin. Pathol Res Pract 189: 902–912
6. Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82: 239–259
7. Brion S, Mikol J, Psimaras A (1973) Recent findings in Pick's disease. Prog Neuropathol 2: 421–452
8. Brion S, Plas J, Jeanneau A (1991) Maladie de Pick. Point de vue anatomo-clinique. Rev Neurol (Paris) 147: 693–704
9. Brun A (1987) Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriatr 6: 193–208
10. Brun A (1993) Frontal lobe degeneration of non-Alzheimer type revisited. Dementia 4: 126–131
11. Brun A, Englund B, Gustafson L, Passant U, Mann DMA, Neary D, Snowden JS (1994) Consensus statement: clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 57: 416–418
12. Collinge J, Palmer MS, Mahal SP, Campbell T, Brown J, Hardy J, Brun AE, Gustafson L, Bakker E, Roos R, Groen JJ (1994) Familial Pick's disease and dementia in frontal lobe degeneration of non-Alzheimer type are not variants of prion disease. J Neurol Neurosurg Psychiatry 57: 762–768
13. Constantinidis J, Richard J, Tissot R (1974) Pick's disease: histological and clinical correlations. Eur Neurol 11: 208–217
14. Cooper PN, Jackson M, Lennox G, Lowe J, Mann DMA (1995) Tau, ubiquitin, αB-crystallin immunohistochemistry define the principal causes of degenerative frontotemporal dementia. Arch Neurol 52: 1011–1015
15. Deymeer F, Smith TW, DeGirolami U, Drachman DA (1989) Thalamic dementia and motor neuron disease. Neurology 39: 58–61
16. Dickson DW, Horoupian DS, Thal LJ, Davies P, Walkley S, Terry RD (1986) Klüver-Bucy syndrome and amyotrophic lateral sclerosis: a case report with biochemistry, morphometrics, and Golgi study. Neurology 36: 1323–1329
17. Filey CM, Kleinschmidt-De Masters BK, Gross KF (1994) Non-Alzheimer fronto-temporal degenerative dementia. A neurobehavioral and pathologic study. Clin Neuropathol 13: 109–116
18. Giannakopoulos P, Hof PR, Bouras C (1995) Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. Acta Neuropathol 89: 346–355
19. Gibb WRG, Lees AJ (1991) Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 54: 388–396
20. Gustafson L (1987) Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr 6: 209–223
21. Gustafson L (1993) Clinical picture of frontal lobe degeneration of non-Alzheimer type. Dementia 4: 143–148
22. Hamos JE, Oblas B, Pulaski-Salo D, Welch WJ, Bole DG, Drachman DA (1991) Expression of heat shock proteins in Alzheimer's disease. Neurology 41: 345–350
23. Hof PR, Bouras C, Perl DP, Morrison JH (1994) Quantitative neuropathologic analysis of Pick's disease cases: cortical distribution of Pick bodies and coexistence with Alzheimer's disease. Acta Neuropathol 87: 115–124
24. Hori A, Volles E, Witzke K, Spaar FW (1983) Pick's disease of early onset with neurologic symptomatology, rapid course, and nigro-striatal degeneration. Clin Neuropathol 2: 8–15
25. Horoupian DS, Thal L, Katzman R, Terry RD, Davies P, Hirano A, Deteresa R, Fuld PA, Petito C, Blass J, Ellis JM (1984) Dementia and motor neuron disease: morphometric, biochemical, and Golgi studies. Ann Neurol 16: 305–313
26. Hudson AJ (1991) Dementia and parkinsonism in amyotrophic lateral sclerosis. Handb Clin Neurol 15: 231–240
27. Jackson M, Lennox G, Ward L, Lowe J (1995) Frontal dementia with MND inclusions without clinical ALS: report of eleven cases. Neuropathol Appl Neurobiol 21: 148–149
28. Jakob H (1979) Die Picksche Krankheit. Eine neuropathologisch-anatomisch-klinische Studie. Monogr Gesamtgeb Psychiatr 23: 1–110
29. Jellinger K, Danielczyk W, Fischer P, Gabriel E (1990) Clinicopathological analysis of dementia disorders in the elderly. J Neurol Sci 95: 239–258
30. Kato S, Hirano A, Umahara T, Kato M, Herz F, Ohama E (1992) Comparative immunohistochemical study on the expression of αB crystallin, ubiquitin and stress-response protein 27 in ballooned neurons in various disorders. Neuropathol Appl Neurobiol 18: 337–340
31. Kato S, Oda M, Hayashi H, Kawata A, Shimizu T (1994) Participation of the limbic system and its associated areas in the dementia of amyotrophic lateral sclerosis. J Neurol Sci 126: 62–69
32. Kirchmair R, Hogue-Angeletti R, Guitarrez J, Fischer-Colbrie R, Winkler H (1993) Secretoneurin – a neuropeptide generated in brain, adrenal medulla, and other endrocrine tissues by proteolytic processing of secretogranin II (chromogranin C). Neuroscience 53: 359
33. Kitamoto T, Muramoto T, Mohri S, Doh-Ura K, Tateishi J (1991) Abnormal isoform of prion protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob disease. J Virol 65: 6292–6295
34. Knopman DS (1993) Overview of dementia lacking distinctive histopathology: pathological designation of a progressive dementia. Dementia 4: 132–136
35. Knopman DS, Mastri AR, Frey WH, Sung JH, Rustan T (1990) Dementia lacking distinctive histological features: a common non-Alzheimer degenerative dementia. Neurology 40: 251–266
36. Kosaka K, Ikeda K, Kobayashi K, Mehraein P (1991) Striatopallidonigral degeneration in Pick's disease: a clinicopathological study of 41 cases. J Neurol 238: 151–160
37. Kusaka H, Imai T (1993) Pathology of motor neurons in amyotrophic lateral sclerosis with dementia. Clin Neuropathol 12: 164–168
38. Lindgren AKH (1952) The pathoanatomical classification of morbus Alzheimer and morbus Pick. Acta Psychiatr Neurol Scand [Suppl] 81: 118–152
39. Lowe J, Errington DR, Lennox G, Pike I, Spendlove I, Landon M, Mayer RJ (1992) Ballooned neurons in several neurodegenerative diseases and stroke contain αB crystallin. Neuropathol Appl Neurobiol 18: 341–350
40. Lowe J, Mayer RJ, Landon M (1993) Ubiquitin in neurodegenerative diseases. Brain Pathol 3: 55–65
41. Luers T, Spatz H (1957) Picksche Krankheit (Progressive umschriebene Großhirnatrophie). In: Scholz W (ed) Handbuch der speziellen pathologischen Anatomie und Histologie, vol XIII/1A (Nervensystem). Springer, Berlin Göttingen Heidelberg, pp 614–715
42. Mann DMA, South PW (1993) The topographic distribution of brain atrophy in frontal lobe dementia. Acta Neuropathol 85: 334–340
43. Mann DMA, South PW, Snowdon JS, Neary D (1993) Dementia of frontal lobe type: neuropathology and immunohistochemistry. J Neurol Neurosurg Psychiatry 56: 605–614
44. Mirra SS, Hart MN, Terry RD (1993) Making the diagnosis of Alzheimer's disease; a primer for practising pathologists. Arch Pathol Lab Med 117: 132–144
45. Morita K, Kaiya H, Ikeda T, Namba M (1987) Presenile dementia combined with amyotrophy: a review of 34 japanese cases. Arch Gerontol Geriatr 6: 263–277
46. Munoz-Garcia D, Ludwin SK (1984) Classic and generalized variant of Pick's disease: a clinicopathological, ultrastructural, and immunocytochemical comparative study. Ann Neurol 16: 467–480
47. Murayama S, Mori H, Ihara Y, Tomonaga M (1990) Immunocytochemical and ultrastructural studies of Pick's disease. Ann Neurol 27: 394–405

48. Neary D, Snowden JS, Northern B, Goulding PJ (1988) Dementia of frontal lobe type. J Neurol Neurosurg Psychiatry 51: 353–361
49. Neary D, Snowden JS, Mann DMA, Northern B, Goulding PJ (1990) Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry 53: 23–32
50. Neary D, Snowden JS, Mann DMA (1993) The clinical pathological correlates of lobar atrophy. Dementia 4: 154–159
51. Okamoto K, Shunsaku H, Yamazaki T, Sun X, Nakazato Y (1991) New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with amyotrophic lateral sclerosis. Neurosci Lett 129: 233–236
52. Perry G, Steward D, Friedman R, Manetto V, Autilo-Gambetti L, Gambetti P (1987) Filaments of Pick's bodies contain altered cytoskelettal elements. Am J Pathol 127: 559–568
53. Schmid KW, Ellis IO, Gee JMW, Darke BM, et al (1993) Presence and possible significance of immunocytochemically demonstrable metallothionein over-expression in primary invasive ductal carcinoma of the breast. Virchows Arch [A] 422: 153–159
54. Schmid KW, Kunk B, Kirchmair R, Tötsch M, Böcker W, Fischer-Colbrie R (1995) Immunohistochemical detection of a novel neuropeptide endoproteolytically processed from secretogranin II, in normal human endocrine and neuronal tissues. Histochem J 27: 473–481
55. Snowden JS, Neary D, Mann DMA, Goulding PJ, Testa HJ (1992) Progressive language disorder due to lobar atrophy. Ann Neurol 31: 174–183
56. Tierney MC, Fisher RH, Lewis AJ, Zorzitto ML, Snow WG, Reid DW, Nieuwstraten P (1988) The NINCDS-ADRDA Work Group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathologic study of 57 cases. Neurology 38: 359–364
57. Tissot R, Constantinidis J, Richard J (1985) Pick's disease. In: Fredericks JAM (ed) Handbook of clinical Neurology: Neurobehavioural disorders. Elsevier Sci Publ, pp 233–246
58. Torrack RM, Morris JC (1986) Mesolimbocortical dementia. A clinicopathological case study of a putative disorder. Arch Neurol 43: 1074–1078
59. Uchihara T, Tsuchiya K, Kosaka K (1990) Selective loss of nigral neurons in Pick's disease: a morphometric study. Acta Neuropathol 81: 155–161
60. Uhl GR, Hilt DC, Hedreen JC, Whitehouse PJ, Price DJ (1983) Pick's disease (lobar sclerosis): depletion of neurons in nucleus basalis of Meynert. Neurology 33: 1470–1473
61. Ulrich J, Haugh M, Anderton BH, Probst A, Lautenschlager C, His B (1987) Alzheimer dementia and Pick's disease: neurofibrillary tangles and Pick bodies are associated with identical phosphorylated neurofilament epitopes. Acta Neuropathol (Berl) 73: 240–246
62. Verity MA, Roitberg B, Kepes JJ (1990) Mesolimbocortical dementia: clinicopathological studies on two cases. J Neurol Neurosurg Psychiatry 53: 492–495
63. Wightman G, Anderson VER, Martin J, Swash M, Anderton BH, Neary D, Mann D, Luthert P (1992) Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. Neurosci Lett 139: 269–274
64. Wikström J, Paetau A, Palo J, Sulkava R, Haltia M (1982) Classic amyotrophic lateral sclerosis with dementia. Arch Neurol 39: 681–686
65. Yashuhara O, Matsuo A, Tooyama I, Kimura H, McGeer EG, McGeer PL (1995) Pick's disease immunohistochemistry: new alterations and Alzheimer's disease comparisons. Acta Neuropathol 89: 322–330
66. Yoshimura N (1989) Topography of Pick body distribution in Pick's disease: a contribution to understanding the relationship between Pick's and Alzheimer's diseases. Clin Neuropathol 8: 1–6