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The evolution and pathology of frontotemporal dementia

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This is a clinicopathologic study of a prospective, clinic-based cohort of patients with frontotemporal dementia (FTD)/Pick complex, who were followed to autopsy. A total of 60 patients with the clinical syndromes of the behavioural variant of FTD (FTD-bv) (*n* = 32), primary progressive aphasia (PPA) (*n* = 22), corticobasal degeneration syndrome (CBDS) (*n* = 4) and progressive supranuclear palsy (PSP) (*n* = 2) at onset, referred to a cognitive neurology clinic who had subsequent post-mortem examination were included. The most common histological variety was motor neurone disease type inclusion (MNDI) (*n* = 18), followed by corticobasal degeneration (CBD) (*n* = 12), then Pick's disease (*n* = 6), dementia lacking distinctive histology (DLDH) (*n* = 6) and PSP (*n* = 3). Others fulfilled the histological criteria for Alzheimer's disease combined with glial pathology (*n* = 6), Alzheimer's disease only (*n* = 4), Lewy body variant (*n* = 2), prion disease (*n* = 1), vascular dementia (*n* = 1) and undetermined (*n* = 1). The most common first syndrome among the MNDI and DLDH (tau negative) pathologies was FTD-bv, but subsequently progressive aphasia (PA), occasionally CBDS and semantic dementia also developed. Tau positive histologies of CBD, PSP and Pick bodies were most frequently associated with PPA onset or CBDS/PSP, but behavioural symptoms were also common. Age of onset was earlier in tau negative cases, but the duration of illness and gender distribution were about the same in all histological variants. Although the tau negative and positive histologies are predicted to some extent by the clinical onset, the extent of the overlap and the convergence of the syndromes in the course of the disease argue in favour of maintaining the clinical and pathological varieties under a single umbrella.

Keywords: frontotemporal dementia; primary progressive aphasia; corticobasal degeneration; progressive supranuclear palsy; Pick's disease

Abbreviations: CBD = corticobasal degeneration (pathology); CBDS = corticobasal degeneration syndrome (clinical); DLDH = dementia lacking distinctive histology; FTD = frontotemporal dementia; FTD-bv = behavioural variant of frontotemporal dementia; FTLD = frontotemporal lobar degeneration; MND = motor neuron disease; MNDI = motor neuron disease type inclusions; PA = progressive aphasia (secondary); PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; SD = semantic dementia

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Introduction

Clinical Pick's disease, more recently referred to as frontotemporal lobar degeneration (FTLD) (Neary *et al.*, 1998), has a spectrum of underlying pathology, which is often considered 'heterogeneous'. An alternative conceptualization considers the pathology related, even though certain distinctions are maintained. Arnold Pick (1892) described the clinical features: mainly progressive aphasia, apraxia and behaviour change in association with frontotemporal atrophy. It was only later that the round, silver staining inclusions were considered characteristic (Onari and Spatz, 1926), and even later essential for the eponymic designation of the disease (Brun, 1987). However, only a fraction of the clinical cases had these 'Pick bodies' and the rest were renamed frontal lobe degeneration of the non-Alzheimer type (Gustafson, 1987; Brun, 1987) while the clinical syndrome was called dementia of the frontal lobe type (Neary *et al.*, 1988). Subsequently,

both the clinical and pathological entities were incorporated into the term frontotemporal dementia (FTD) (Lund and Manchester Groups, 1994). Primary progressive aphasia (PPA) was considered a distinct entity (Mesulam, 1987). An integrative approach based on clinicopathologic correlation suggests that not only do FTD and PPA overlap clinically and pathologically, but the extrapyramidal component, commonly described as corticobasal degeneration syndrome (CBDS) should be considered part of the overall entity named Pick complex (Kertesz *et al.*, 1994).

Corticodentatonigral degeneration described by Rebeiz *et al.* (1968), subsequently renamed corticobasal degeneration (CBD) (Gibb *et al.*, 1989), was recognized to have frequent language and personality changes, and pathological similarity to Pick's disease. Furthermore, cases presenting with progressive aphasia and the behavioural variant of FTD (FTD-bv) frequently developed CBDS (Kertesz *et al.*, 2000*a*). Progressive supranuclear palsy (PSP) (Steele *et al.*, 1964), characterized by vertical gaze palsy, rigidity, instability and dementia, shows considerable clinical, pathological, biochemical and genetic overlap with CBD/CBDS. A work group on FTD and Pick's disease (McKhann *et al.*, 2001) included CBD and PSP among the pathological substrates of the clinical syndromes of FTD, recognizing that each pathological entity can manifest itself with either language or behaviour disorder, thus incorporating the basic claims of the Pick-complex concept. The concept was reinforced by the discovery that mutations on the Tau gene could produce many of the pathological and clinical varieties identified in sporadic cases.

Currently, clinicopathologic studies recognize that ubiquitinated, tau and synuclein negative inclusions, or motor neuron disease type inclusions (MNDI) (Jackson *et al.*, 1996) are also common in the cortex in FTD/Pick complex (Munoz 1998, Munoz *et al.*, 2003*a*, Hodges *et al.*, 2004), In addition, dementia lacking distinctive histology (DLDH) is applied when tau or ubiquitin positive inclusions are lacking (Knopman *et al.*, 1990). All types include lobar atrophy, neuronal loss, gliosis, superficial spongiosis, and often ballooned neurons, and some glial abnormality. Distinctive histological abnormalities include Pick bodies, the CBD/PSP type neuronal inclusions, motor neurone disease type inclusions (Jackson *et al.*, 1996) and several astrocytic tau inclusions (Munoz, 1998). A range of histochemical abnormalities is found not only across the clinical phenotypes, but also among families with the same mutation, and even within a brain. Conflicting information about the duration of illness and sex differences between the pathological and clinical varieties have been published and additional demographic data are needed from autopsy specified cohorts. Recently the combined clinicopathologic experience from two centres, Cambridge and Sydney, provided the first large overview of the features of an autopsy-based population (Hodges *et al.*, 2003, 2004), with similarities and differences from this study discussed below.

This is a study of a clinic-based cohort of FTD/Pick complex patients, who were prospectively followed to autopsy. This includes not only FTLD, as defined by Neary *et al.* (1998), but also the CBDS/PSP syndrome. Most patients were followed yearly and substantial clinical, behavioural, cognitive and neuroimaging information has been collected. The clinical syndromes and their correlation with the histological varieties are surveyed in an effort to describe the natural course of FTD/Pick complex, the evolution of the clinical syndromes that came to pathology and uncover whether patterns in the clinical syndromes predict pathology.

Methods

Patients

Patients (n = 60) were included if they had been studied at the cognitive neurology clinic or in the University of Western Ontario dementia study in London, Ontario, during the years 1990–2004 and met the clinical criteria described below and came to autopsy.

FTD-bv presented a progressive deterioration of behaviour and personality (Neary *et al.*, 1998). We also included four patients, who were autopsied before 1990 and did not have the clinical diagnosis of FTD-bv, but had enough clinical information to fulfil the criteria. Two of these patients were members of a family published as 'long duration spongiform encephalopathy' (Rice *et al.*, 1980) and subsequently as a family with probable genetic linkage to chromosome 17, but with tau negative, ubiquitin positive inclusions (Kertesz *et al.*, 2000*b*). One patient was diagnosed as 'dementia with frontal features' and one from the University of Western Ontario dementia study diagnosed as atypical dementia, but both had documented onset with behavioural symptoms, followed by aphasia.

Semantic dementia (Snowden *et al.*, 1989) patients were defined by a prominent comprehension deficit, naming difficulty and asking the meaning of nouns and objects. In this series this was only seen in patients as a second syndrome after onset with a behavioural disturbance. We do have patients with primary semantic dementia but as yet they have not come to autopsy.

PPA (Mesulam, 1987) was diagnosed as probable when aphasia was the first syndrome. This group included anomic, logopenic and non-fluent patients as described in detail previously (Kertesz *et al.*, 2003). 'Possible PPA' was a separate category if the history of onset included memory loss ('forgetting words' that was difficult to distinguish from language change), but these patients were prominently aphasic by the time they were seen. The patients with possible PPA had Alzheimer's disease in the clinical differential diagnosis. We use 'PA' to designate progressive aphasia developing as a second or third syndrome.

CBDS exhibited unilateral rigidity, apraxia and 'alien hand' with or without additional features of PSP (see below). In these patients the extrapyramidal symptoms developed first and were followed by cognitive change. Cases with cognitive syndrome first, who developed CBDS or PSP later, were included under the primary cognitive onset, and the motor disorder was documented under secondary and tertiary syndromes.

PSP showed vertical gaze palsy, falling, axial rigidity and pseudobulbar palsy. Since the clinical and pathological overlap with CBD/CBDS was substantial, these syndromes were combined in some of the calculations.

Patients were followed annually with neurological, neuropsychological and behavioural testing. Telephone follow-up was obtained when patients were unable to attend the cognitive neurology clinic.

Onset was determined by history, most often from informants, and the clinical features confirmed at the first clinic presentation. Onset of second and third syndromes in the interval between clinic visits was also determined by history and confirmed by examination. Occasionally signs (such as unilateral rigidity or verbal apraxia) would highlight a new syndrome, but with questioning symptoms were also usually apparent and served as the marker for duration. The time between the first and second and third syndromes is indicated in years (mean and standard deviation in Figs 3 and 4). Referrals came mainly from the London, Ontario area; about a third were already diagnosed as suspected FTD or PPA. The others were referred with a diagnosis of Alzheimer's disease, vascular or atypical dementia, and a few were sent as cases of suspected stroke or parkinsonism. The diagnosis was based on history and neurological examination primarily, with behavioural inventory, language and other cognitive tests and neuroimaging as supportive evidence. All caregivers were approached for provisional autopsy consent either at the first or on subsequent visits. The cases with autopsy represent 20% of patients seen with these clinical features.

Neuroimaging, usually MRI or CT and SPECT, was obtained at the first visit and subsequently if possible. Some patients had yearly neuroimaging with formal neuropsychological assessment. Frontotemporal atrophy, often asymmetrical, supported the diagnosis, but patients were not selected on the basis of neuroimaging. Neuropsychological testing included screening with the mini mental state examination (MMSE), Mattis Dementia Rating Scale (DRS), clock drawing, logical memory, visual and verbal learning, frontal lobe executive tests, such as Wisconsin Card Sort Test, Trial Making A and B and the Stroop Test, language test with the Western Aphasia Battery, the Palms and Pyramids tests for semantic dementia and the caregiver-based Frontal Behavioural Inventory (Kertesz *et al.*, 2003). The patterns of relatively preserved episodic memory and visuospatial cognition, language impairment and the cut off score of $\geq$30 on the FBI contributed to the diagnosis, but were not used as criteria.

Neuropathology

Neuropathological examination was carried out by one of the authors (D.G.M.), in 38 cases, and in the remainder, slides or reports were reviewed. Histological methods included Bielschowsky and Gallyas silver stains, and immunostains for tau, (Tau-2, Sigma-Aldrich, AT8, Innogenetics) alpha-synuclein (gift of Dr Masliah) and ubiquitin (U5379, Sigma with a few exceptions as indicated) and prion protein immunostains where appropriate. Criteria for histological classification of FTD have been detailed elsewhere (Munoz, 1998; Munoz *et al.*, 2003*a*) and substantially follow the report of the Work Group on FTD and Pick's Disease (McKhann *et al.*, 2001). In summary, dementia with Pick bodies (Pick's disease) was characterized by round or oval, compact intracytoplasmic neuronal inclusions stained by Bielschowsky but not by Gallyas, tau immunoreactive and located in dentate fascia, hippocampus and cerebral cortex. CBD was characterized by ballooned achromatic neurons (Pick cells), tau immunoreactive, intracytoplasmic neuronal inclusions of variable morphology, stained by both Bielschowsky and Gallyas, pervasive grey and white matter threads, and abundant tau positive glial pathology, both coils in oligodendrocytes, and glial plaques in astrocytes. PSP differed from CBD by the predominantly subcortical distribution of the neuronal pathology, and the presence of tufted astrocytes instead of glial plaques. The diagnosis of FTD with MNDI (Jackson *et al.*, 1996) which are tau and synuclein negative; ubiquitin positive (ITSNU, Munoz, 1998) rested on the presence of these structures in the cytoplasm of neurons in the fascia dentata and cerebral cortex, here usually accompanied by ubiquitinated dystrophic neurites. DLDH was diagnosed when only superficial linear spongiosis, neuronal loss and gliosis could be identified. Three cases in which ubiquitin immunostains could not be obtained because the blocks were not available to us were included by default in this group. Criteria for the histological diagnosis of Alzheimer's disease were those of the NIA–Reagan panel (Ball *et al.*, 1997).

Statistical methods

Demographic information that included age of onset, duration and education were analysed among the groups using one-way ANOVA. *Post hoc* analyses were done using Tukey's honestly significant difference test. Fisher's exact probability test and χ^2-tests were used to analyse the gender distributions among the groups and the relationships between clinical syndromes and pathology. The log rank test was used to analyse for differences in survival. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v.10.1 for Windows, Chicago, IL) and alpha level was set at 0.05 (2-tailed).

Results

Pathology

A total of 60 autopsied patients with the clinical diagnosis of Pick complex as defined in the methods were included. Forty-five had pathology compatible with FTD/Pick complex. The most common neuropathologic variety was MNDI (n = 18). The second most common histology was CBD, (n = 12). One case reported as 'resembling FTDP-17 pathology' was classified with the CBD group because of the substantial tau positive glial and neuronal pathology, including glial plaques, even though ubiquitin positive tau negative inclusions were also seen. So far no linkage or tau mutation has been found in that family. PSP was also seen, but less frequently (n = 3) and often overlapping with CBD pathology. Pick body dementia (Pick's disease) (n = 6) was relatively uncommon. DLDH was also a less common pathology (n = 6) although the actual number may be even lower as three cases were included by default without evaluation of ubiquitin immunoreactivity.

Ten autopsies fulfilled the criteria for Alzheimer's disease, nine of which had the clinical diagnosis of possible PPA, because of early memory loss accompanying the language disturbance. Six of these had tau immunoreactive 'thorny astrocytes' (Munoz *et al.*, 2003*b*). The remaining five patients form a heterogeneous group. One with a combination of cortical Lewy body and Alzheimer pathology manifested with FTD-bv. Another with Lewy body pathology began as 'possible' PPA without developing additional syndromes. One showed extensive subcortical ischaemic encephalopathy, so called Binswanger's disease, and also manifested with FTD-bv. One received the pathology diagnosis of Gerstmann–Straussler–Scheinker prion disease, and presented with FTD-bv followed by CBDS and PA clinically. Finally, a patient with florid behavioural symptoms died a few days after an accident sustained while riding a motorcycle without a license. The autopsy showed numerous contusions, haematomata, and axonal swellings, but a normal brain weight and neither

Table 1 Subject demographics, syndrome frequencies and intervals according to pathology subtypes

	N	Gender M : F	Age of onset, mean (standard deviation)	Years to second syndrome, mean (standard deviation)	Years to third syndrome, mean (standard deviation)	No. of syndromes, mean (standard deviation)	Duration, mean (standard deviation)
Tau negative	24	12 : 12	54.3 (9.7)*,†,‡	3.2 (2.3)	5.5 (3.0)	2.1 (0.6)*,†,‡	7.9 (3.6)
MNDI	18	7 : 11	54.4 (9.8)	3.4 (1.9)	4.8 (2.8)	2.2 (0.6)	8.6 (3.6)
DLDH	6	5 : 1	53.8 (10.3)	2.6 (3.6)	9.0 (–)	2.0 (0.6)	5.8 (3.3)
Tau positive	21	12 : 9	62.8 (6.9)*,†	3.2 (4.5)	5.2 (5.9)	2.7 (0.5)*,†,§	8.0 (5.1)
CBD	12	8 : 4	63.8 (7.8)	3.7 (5.7)	5.8 (7.4)	2.8 (0.5)	7.4 (6.3)
Pick's	6	3 : 3	60.7 (6.2)	3.5 (1.8)	5.0 (2.6)	2.8 (0.4)	10 (3.0)
PSP	3	1 : 2	63 (5.0)	0.3 (0.3)	0.5 (–)	2.3 (0.6)	6.3 (1.5)
Pick complex total	45	24 : 21	58.2 (9.5)	3.2 (3.5)	5.3 (5.2)	2.4 (0.6)	8.0 (4.3)
Alzheimer's disease	10	5 : 5	64.1 (10.4)*,‡	–	–	1.1 (0.3)*,‡,§	8.6 (2.3)

*One-way ANOVA, $P < 0.05$. †,‡,§Pairwise comparisons, $P < 0.05$.

evidence of cortical atrophy nor evidence of deposition of tau or ubiquitin.

The pathological varieties, their demographic details as well as the number of clinical syndromes and the intervals between them are summarized in Table 1. For statistical purposes, FTD/Pick complex patients have been grouped into those with tau deposition (CBD, PSP, Pick body), as tau positive, those without (MNDI and DLDH) as tau negative and the Alzheimer's disease cases. Tau negative patients were younger at onset than tau positive ones (*post hoc*, $P = 0.006$) and the Alzheimer's disease cases (*post hoc*, $P = 0.013$). The Alzheimer's disease pathology group had fewer additional syndromes develop compared to FTD/Pick complex cases. There were no significant differences in gender distribution between the pathology groupings on χ^2-test. The prognosis of the tau positive, tau negative and other pathology groups was the same according to the survival curves (Fig. 1).

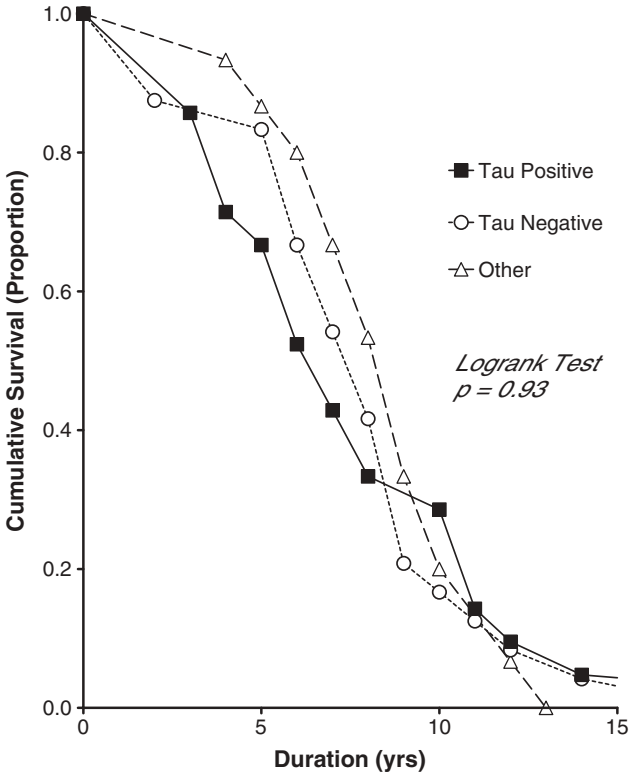

Fig. 1 Survival curves according to underlying tau-positive and tau-negative pathologies. The log rank test found no significant difference between the pathology groups.

The clinical syndromes and their evolution

The clinical syndromes at onset (first syndrome) and their evolution (the second and third syndromes appearing in the patients) were compared between the histological varieties (Fig. 2). FTD-bv was the most common first syndrome in the MNDI pathology group ($n = 14$), followed by PA ($n = 4$). PPA ($n = 5$) was the most common first syndrome among the CBD histological variety followed by FTD-bv ($n = 4$). PA was also the most common secondary syndrome ($n = 4$) for this pathology. Only one of the MNDI patients developed typical, devastating MND, two others had amyotrophy, and another two had late appearing, mild MND manifesting with up-going toes, hyperreflexia and dysphagia. Many others however died choking on food, possibly with unproven bulbar MND, or loss of frontal control of swallowing.

The results of longitudinal clinical follow-up in the other pathological categories showed that three out of the six cases of Pick body dementia had PPA and three had FTD-bv, at onset, but three developed CBDS as the second syndrome and FTD-bv as the third. The six cases of DLDH each presented at onset with FTD-bv and only one developed MND as the tertiary syndrome. (This case did not have ubiquitin staining, and may have had MNDI pathology). PSP type pathology was associated with PSP and CBDS at onset and secondary syndromes were PA ($n = 1$) and FTD-bv ($n = 2$). Among those with Alzheimer pathology and other histologies the most common first syndrome was PPA ($n = 10$). Six of these had tau positive glial pathology in addition to Alzheimer's disease. One of these developed a movement disorder. Of those beginning with FTD-bv ($n = 5$), one case with GSS pathology developed a movement disorder followed by progressive aphasia while the other four showed no additional

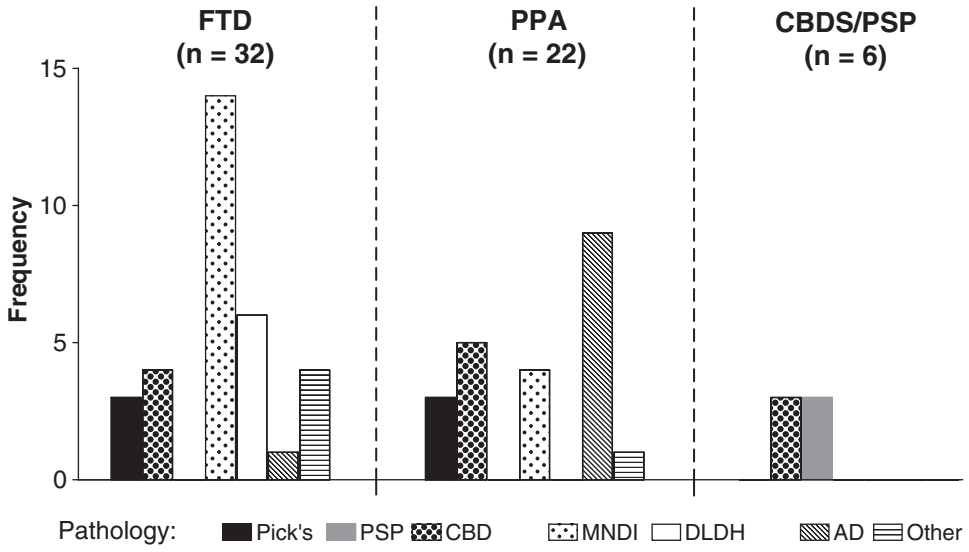

Fig. 2 The frequency of each pathology according to the first clinical syndrome.

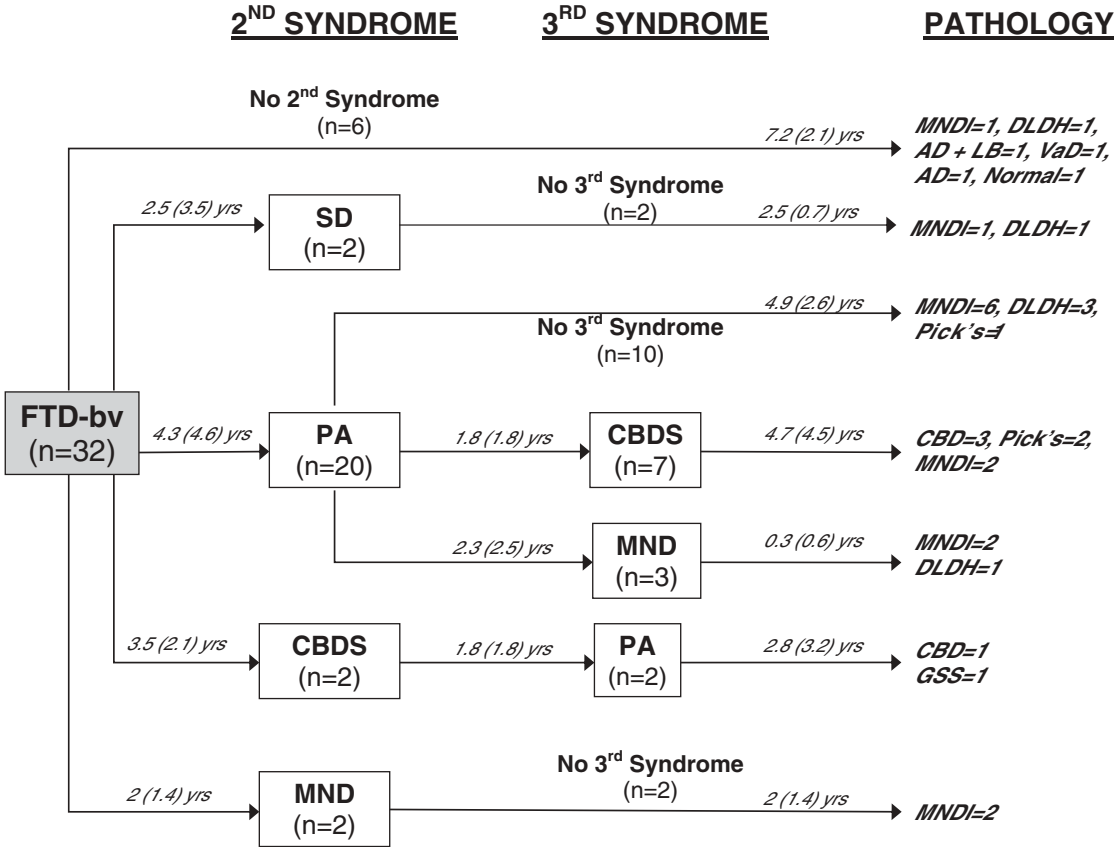

Fig. 3 The evolution of clinical syndromes and final pathology in cases beginning with FTD. The average intervals (and SDs) between syndromes are expressed in years.

syndromes. Onset with a movement disorder was not seen with these pathologies.

The evolution of the clinical syndromes grouped by symptoms at onset is illustrated in Figs 3–5. FTD-bv was the most common first syndrome ($n = 32$) followed in time by PA in the majority of cases ($n = 20$) and less often by CBDS ($n = 2$) (SD = 2) and MND ($n = 2$) (Fig. 3). Notably the six patients who had no secondary syndromes after FTD-bv, included most of the false positive diagnoses, one Alzheimer's disease, one LBD, one vascular dementia and one 'normal'. The second most common first syndrome ($n = 22$) was PPA and 10 of these patients had no secondary syndrome (Fig. 4). Nine of these

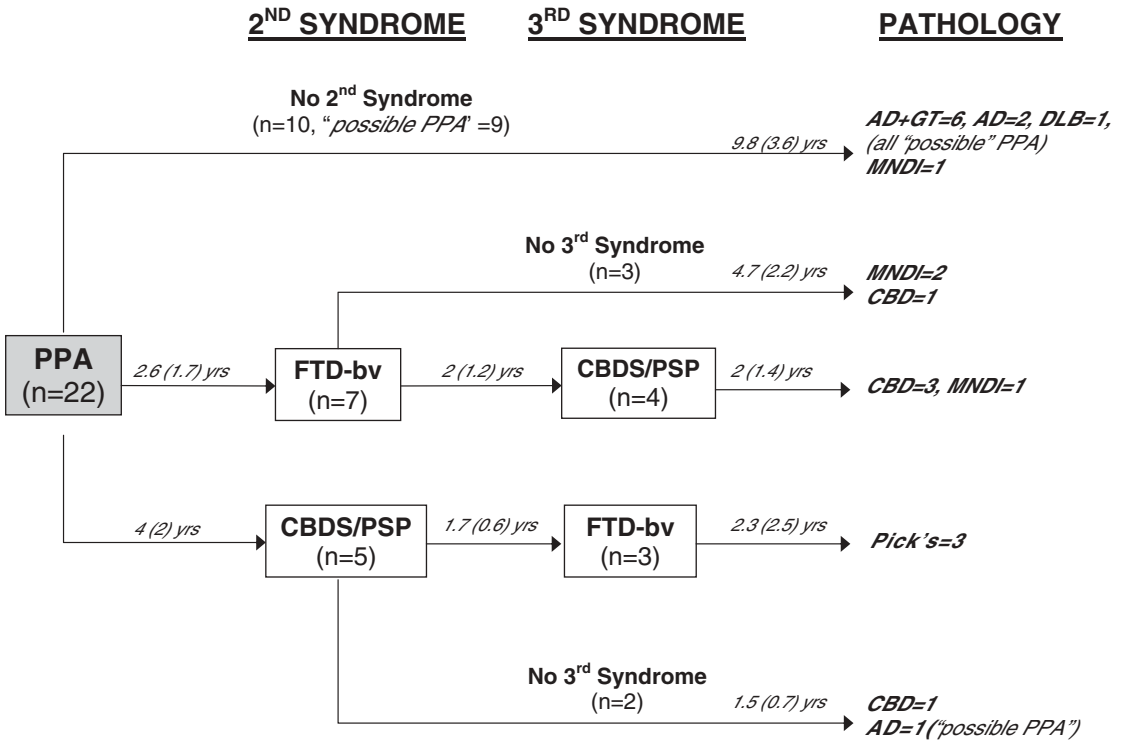

Fig. 4 The evolution of clinical syndromes and final pathology in cases beginning with PPA.

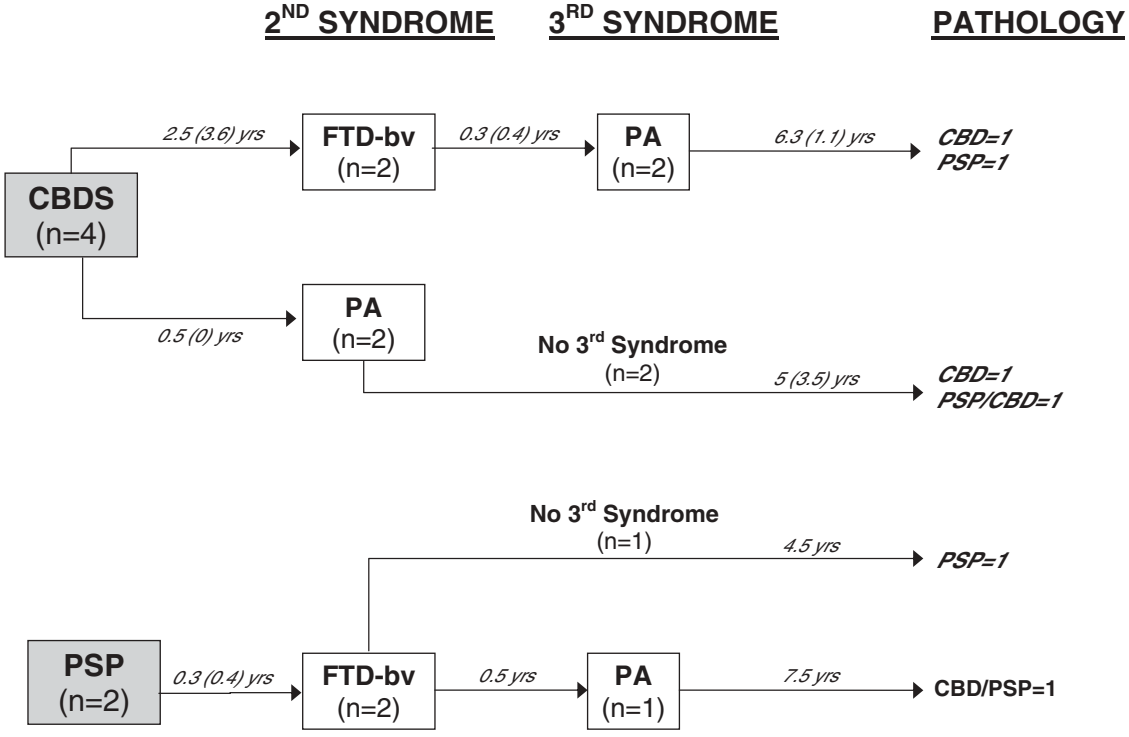

Fig. 5 The evolution of clinical syndromes and final pathology in cases beginning with a movement disorder.

were classified as 'possible', because of atypical features, such as memory loss. Their pathology was Alzheimer's disease, with the additional finding of thorny astrocytes in six. Typical PPA was often followed by FTD-bv (n = 7) and CBDS/PSP (n = 5). Six CBDS/PSP onsets were followed by FTD-bv (n = 4) and PA (n = 2), sometimes almost simultaneously (Fig. 5).

An analysis (Fig. 6) of the frequency of clinical syndromes contrasts the tau positive autopsies with the combined tau

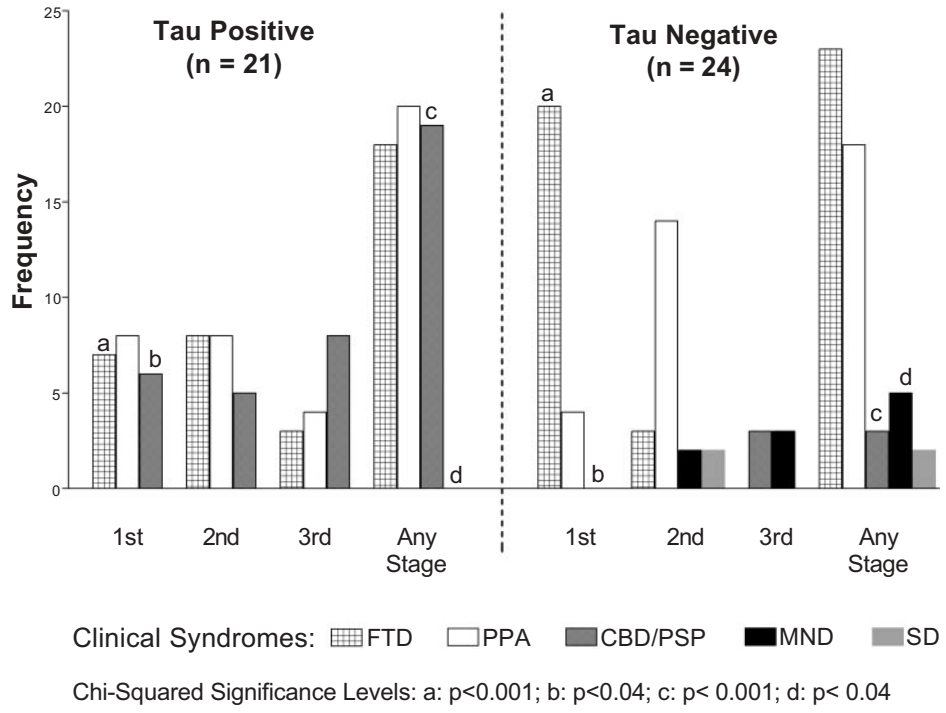

Fig. 6 The frequency of clinical syndromes at each stage according to tau positive and negative histologies.

negative varieties at different stages. FTD-bv onset was by far the commonest in tau negative pathology, while PPA was more predictive of tau positive pathology, most of which in this series were CBD. MND occurred only in the tau negative group, while CBDS was infrequent (three cases only) with this pathology.

Age, gender, education, duration of illness and familial incidence in the clinical groups

The age at onset, gender distribution and duration until death were also analysed by clinical groupings of the FTD/Pick complex (Table 2). There is a significant age of onset difference between the FTD-bv, PPA, and CBDS/PSP groups on ANOVA, and *post hoc* pairwise comparison is significant between FTD-bv and PPA. No significant differences were found in gender distribution, duration or education between the clinical groupings. In cases with Alzheimer's disease and other pathologies who began with FTD-bv or PPA, the ages of onset and duration were similar to those of FTD/Pick complex, but they were distinguished by the lower number of second and third syndromes with follow-up. Fifteen of the 45 cases or 33% with Pick complex pathology had a definite family history of the disease. Nine cases had tau negative pathology and six were tau positive. The number of the tau negative group was inflated by including four members of a Mendelian dominant pattern family. As a group the familial cases were significantly younger than the others (mean age at onset = 53.1, SD = 10.3 versus 60.8, 8, $P < 0.05$), but excluding them from the overall analysis does not alter basic demographic comparisons between tau positive and negative cases. Survival curves with the log rank test showed no significant difference in the duration and course between the clinical groups defined by the type of onset (Fig. 7).

Table 2 Demographics among pathologic groups according to clinical onset

	N	Gender M : F	Age of onset, mean (standard deviation)	Duration, mean (standard deviation)
First syndrome in FTD/Pick complex				
FTD-bv	27	16 : 11	54.8 (9.4)*†	8.3 (4.8)
PPA	12	6 : 6	63.8 (8.3)*†	7.8 (4.0)
CBDS/PSP	6	2 : 4	62.7 (3.7)*	7.0 (3.1)
Total	45	24 : 21	58.2 (9.5)	8.0 (4.3)
First syndrome in Alzheimer's disease + other				
FTD-bv	5	3 : 2	55.4 (12.1)	8.2 (3.4)
PPA	10	5 : 5	63.1 (10.3)	8.8 (2.3)
Total	15	8 : 7	60.5 (11.1)	8.6 (2.6)

*One-way ANOVA, $P < 0.05$. †Pairwise comparison, $P < 0.05$.

Discussion

The clinical syndrome of FTD/Pick complex has a range of underlying pathology, but the main division appears to be along tau negative and tau positive histochemistry, in addition to the differences in the cortical and subcortical distribution of the lesions. The most common histological picture in this series is characterized by ubiquitinated inclusions that are tau and synuclein negative, first described in the spinal

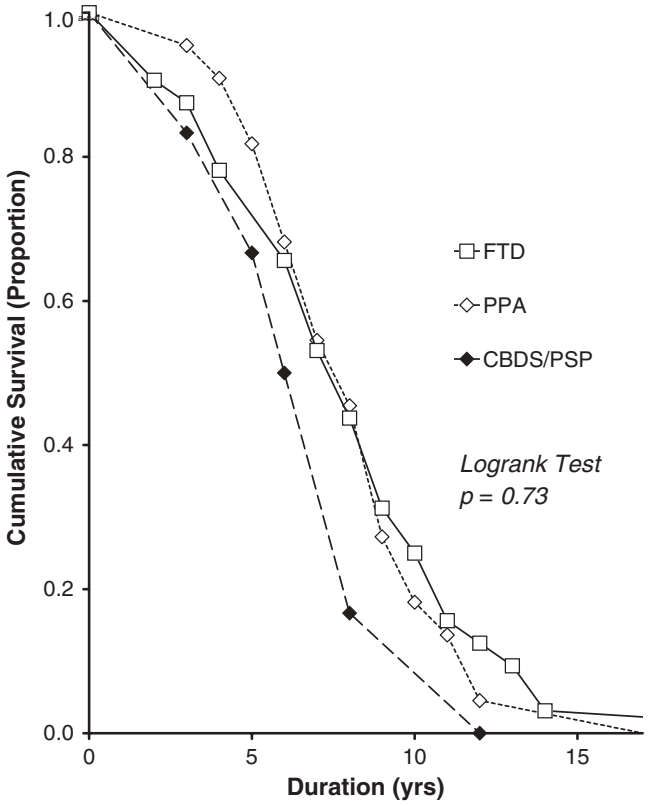

Fig. 7 Survival curves from symptom onset according to first clinical syndrome. The Log rank test found no significant differences between the clinical groups.

cord of ALS patients (Okamoto *et al.*, 1991) and also called motor neurone disease type inclusions (MNDI, Jackson *et al.*, 1996). This prospective study of a clinical cohort, provides important confirmation of the initial impression of relatively high incidence of this variety (Munoz, 1998). The combined Cambridge and Sydney experience (Hodges *et al.*, 2004) had an equal number of the MND-type inclusions and DLDH-type pathology. Their most common histopathology was Pick's disease with Pick bodies and the combined tau positive pathology outnumbered the tau negative cases. The identification of Pick bodies and thus the incidence of Pick's disease depends on the morphology, silver technique (Gallyas) reactivity and distribution of the inclusions (Dickson, 1998; Munoz, 1998), or tau repeat number specific antibodies not available to most laboratories. This is a possible explanation of the variable ratio of Pick's disease to CBD, which was high in the Cambridge/Sydney study (Hodges *et al.*, 2004) and lower in this study.

The clinical syndrome most frequently seen with MNDI is the behavioural onset, which may include features of semantic dementia. We have identified two cases of prominent semantic dementia after the onset of behavioural abnormalities, and these were included with the FTD-bv onset group. One of them had MNDI and the other DLDH pathology, both tau negative. We are following several patients with primary semantic dementia clinically but they have not come to autopsy. Although there is a trend to expand the diagnosis of semantic dementia, our conservative definition includes patients only if their comprehension deficit is prominent and they question the meaning of words heard in conversation ('What is parade? . . . shoe-polish? . . . steak? . . . etc.'). PPA and the movement disorder of CBDS/PSP also occur with MNDI. In fact we found three instances when such a movement disorder was associated with tau negative pathology, albeit in some only appearing late in the course of their illness. Such cases have been reported sporadically in the literature (Grimes *et al.*, 1999; Paviour *et al.*, 2004). Three of our six DLDH cases did not have ubiquitin staining and may well have had MNDI. There were three cases where even ubiquitin antibodies failed to show distinctive histology. These patients also had predominantly behavioural onsets and they were grouped with MNDI clinically and pathologically in the tabulation of the clinical syndromes with tau negative pathology.

The second most frequent histological variety was CBD (n = 12), and the clinical onset in this group was evenly distributed between the behavioural (n = 4), aphasic (n = 5) and movement disorders (n = 3). These findings suggest that CBD is as frequently the pathological substrate of FTD-bv and PPA as of the clinical CBDS in our cohort of patients. Eventually most patients with CBD pathology had developed clinical CBDS or PSP, or features of both, with the exception of one patient, who died early with cancer. Longitudinal follow-up is necessary to appreciate the frequent late occurrence of the extrapyramidal features. Another smaller pathological series from a brain bank have suggested also that the most common presentation of CBD pathology was 'dementia' (Bergeron *et al.*, 1998). The high frequency of progressive aphasia onsets in CBD confirms previous data (Kertesz *et al.*, 1994; Kertesz and Munoz, 2003; Graham *et al.*, 2003). The clinical diagnosis of PSP often overlaps with CBDS as they share the extrapyramidal features especially the bradykinesia, falling and gaze palsy, and patients may have features of both. The diagnosis may change as the patient develops new symptoms. Similarly pathologists may report transitional cases with both diagnoses. In one of the three PSP reports, pathological features of both PSP and CBD were listed. Furthermore, another case had both features of CBD and MNDI indicating the possibility of transitional patterns between the tau positive and negative varieties.

Recruitment bias may influence the distribution and frequency of the clinical and pathological varieties of the cases. Although our interest in FTD is well known, we have a general cognitive clinic with ~50% of our patients identified as Alzheimer's disease. Our clinical FTD cohort, from which this study is derived, has about equal numbers of aphasic and behavioural onsets, although our interest in aphasia may influence referrals. This includes a significant number of 'possible PPA' cases, with prominent aphasia (fluent at the beginning and non-fluent at later stages), but also a history of memory loss at onset who may be diagnosed as Alzheimer's disease initially. These patients also tend to be older, but this

is not always the case. Alzheimer's disease with focal glial tau pathology, particularly with thorny astrocytes, represents a distinct substrate of this 'possible progressive aphasia' syndrome (Munoz *et al.*, 2003*b*). The nosological position of these cases remains to be elucidated. They may represent a combination of Alzheimer's disease with the glial pathology of Pick complex. Similar cases were described sporadically (Karbe *et al.*, 1993; Mesulam *et al.*, 2003) and as atypical Alzheimer's disease (Galton *et al.*, 2000).

The methodological problems of a clinicopathologic study of a clinic-based cohort, are numerous, and limit the extent to which the aims of the study can be accomplished. The distribution of the clinical syndromes depends on the diagnostic consistency and the quality and length of the follow up. There is an ongoing debate about the definition of both the clinical and the pathological phenotypes. However, we made an attempt to use consistent criteria at the same time as considering the significant developments in the field. We feel that the study confirms the concept of clinically identifiable syndromes that overlap in time to a considerable extent. The relationship of the pathological varieties remains controversial. Some consider it a heterogeneous collection, others a related spectrum. Overall, several observations can be made about the underlying pathology according to the onset and evolution of clinical syndromes. While tau negative is the most common pathology among those with FTD-bv onset, the subsequent development of a movement disorder increases the likelihood of tau positive pathology (3 : 1). Also, the progression from FTD-bv to PA without a third syndrome or the development of MND at any stage after onset virtually ensures tau negative pathology (16 : 1). Conversely, a movement disorder at onset or one developing after an aphasic onset greatly reduces the likelihood of tau negative pathology at autopsy (1 : 13).

Argyrophilic grain disease, and neuronal intermediate filament inclusion disease were not encountered in this series. The nosological status of these conditions is as yet indeterminate. The use of alpha-internexin antibodies has shown positivity in a number of conditions and recently an association with FTD/Pick complex was suggested (Cairns *et al.*, 2004). Excluding those cases with co-existing Alzheimer's disease and glial tau ($n = 6$), four cases of Alzheimer's disease without glial pathology, two cases with the Lewy body variant of Alzheimer's disease, one case with GSS, one case with subcortical vascular pathology and one normal brain represent nine cases (15%) of false positive diagnoses, providing an 85% specificity for the clinical designation of FTD/Pick complex. On reviewing the clinical features of these cases, the diagnosis of FTD was not supported by neuroimaging in three patients. Both Lewy body patients were considered atypical clinically; one had periventricular white matter changes and the diagnosis alternated between PPA, vascular dementia and PSP, because of stiffness, falling and upward gaze palsy. The other was older, had memory loss and responded well to a cholinesterase inhibitor. Three neurologists diagnosed the GSS case as FTD, but the periodic frontal slow waves on the EEG were overlooked and the jerky tremor attributed to CBDS. The subcortical vascular case mimicked FTD-bv except for hypertension and moderate white matter hyperintensities on the MRI. Nevertheless, the finding of Binswanger's disease was a surprise to us because this case had none of the clinical features of vascular dementia. These few exceptions rather than indicating heterogeneity of pathology, underline the fallibility of clinical diagnosis. Nevertheless, the clinical pattern predicts FTD/Pick complex pathology in the majority of patients.

The average age of onset is ~10 years lower in the tau negative cases than in the Alzheimer's disease group (with 'possible PPA') and also significantly lower than the tau positive group. The younger age of onset seems an important clinical feature especially in FTD-bv and less so in PPA and CBDS who tend to be older when the disease strikes them, and especially if they have an underlying tau positive pathology. This confirms the trend from other publications (Hodges *et al.*, 2003; Kertesz and Munoz, 2003). There were no gender or education differences between the tau negative, tau positive and overall groups, but CBD occurred in twice as many males and DLDH had five males to one female. These differences are probably related to the smaller sample size. We did not find significant gender differences between the clinical syndromes either, contrary to other reports in the literature (Hodges *et al.*, 2003). The lack of gender difference in the overall disease complex is similar to a large survey study in The Netherlands published recently (Rosso *et al.*, 2003). The duration of illness from onset to death is the same in the tau positive and negative cases, contrary to another report (Hodges *et al.*, 2003). Although some believe that FTD/Pick complex patients have a more malignant course and shorter duration of illness than Alzheimer's disease patients, the evidence from the present study would suggest caution in the interpretation of the differences. Undoubtedly, the development of MND, dysphagia and immobility are indications of poorer prognosis and the lower survival rates may be related to the higher incidence of clinical MND in other studies (Hodges *et al.*, 2003), but this is not the same as the high incidence of MND type inclusions in this study. We only had one patient with FTD-bv and MNDI who developed full-blown MND within a year from onset and died a year later.

Conclusions

The longitudinal follow-up to autopsy of 60 patients with FTD-bv, PPA, CBDS and PSP discloses a major distinction based on the presence or absence of abnormally phosphorylated tau in neuronal cytoplasmic inclusions and glial structures. Progressive aphasia and CBDS present more frequently with the tau positive histology (tauopathies) comprising CBD/PSP/Pick's, while the behavioural variety of FTD is more frequent with the tau negative MNDI type of ubiquinopathies and DLDH. However, there are many exceptions to this dichotomy and it may be premature to split the complex clinically or pathologically. The finding of clinical CBDS with pathologies other than CBD is an example of this

overlap and discourages the prediction of the pathological variety from the clinical phenotype with certainty. The observations suggest that the syndromes, albeit initially distinct, converge over time in a single patient, and that they can be the manifestation of different histological varieties.

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