Supplementary material for Manuscript ID jnnp-2013-306948, resubmitted 26 November 2013

New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications

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Supplementary Methods

Case ascertainment - 178 consecutive neuropathologically-ascertained cases with an initial clinical diagnosis of a FTD syndrome were collected by the University of Cambridge Brain Bank, England (n=107) and the Sydney Brain Bank, Australia (n=71) through multidisciplinary research programs longitudinally investigating neurodegenerative diseases. As detailed in the methods, inclusion criteria for this study was an initial clinical diagnosis of a FTD syndrome (bvFTD, semantic dementia and progressive non-fluent aphasia)[3, 4] and a confirmatory neuropathological diagnosis or a pathological diagnosis of AD. Patients with co-existing motor impairments were not excluded from the analysis, but a dominant motor disorder was an exclusion criteria.

All Cambridge and the majority of Sydney cases underwent standardised neuropsychological testing although the tasks used varied over the 20 years of patient ascertainment. All Cambridge cases were seen by the same experienced clinician (JRH) who used the language assessment as described in Cognitive Assessment for Clinicians (ADD REF TO BOOK), later formalised as the Progressive Aphasia Language Scale (PALS)[1]. Other testing typically included tests of memory (Logical Memory/Story Recall, Warrington Recognition Memory

Test, Recall Rey Complex Figure), visuospatial function (Rey Copy Figure, Visual Object and Space Perception Battery), language (Cookie Theft test, TROG, Cambridge Semantic Memory Battery [2]) and executive function (Trials, Stroop Test, Wisconsin Card Sorting Test, letter fluency, Raven's Coloured Matrices/Raven's Progressive Matrices). The results of these tests were considered in assessing the presence, or absence, of memory and executive deficits.

Case selection using retrospective application of revised diagnostic criteria [3, 4] **-** For this study, cases who had a complete set of detailed clinical (all had neurological examinations and medical history, brain imaging and more specialized reports available for a subset), neuropsychological assessments and informant interviews (n=104 in Cambridge; n=62 in Sydney) were reviewed by LC and the revised criteria retrospectively applied. LC was unaware of the pathological diagnosis and had not been involved with the patients' management. Particular attention was paid to the first clinical assessment and diagnosis, the date of diagnosis, and onset of symptoms as reported by the family and all features characteristic of one of the clinical variants of FTD (Table 1) identified. There was a small proportion (n=22) of PPA cases that presented with mixed features and were deemed difficult to retrospectively classify, and for these cases additional inter-rater reliability with a neurologist (CL) blinded to initial clinical and neuropathological diagnosis was performed with 91% (20/22) concordance. A revised diagnosis by consensus (LC and JH) was reached for all cases. In total 30 cases (n=4 in Cambridge; n= 26 in Sydney) were excluded due to the absence of sufficient clinical information to classify them using the new criteria, leaving 135 screened cases (96 from Cambridge and 39 from Sydney) for inclusion in this study.

Statistical plan and analysis - A series of analyses were performed to assess

1) whether case ascertainment from different clinical cohorts affected the range of FTD syndromes observed using the new criteria – differences in the prevalence of clinical groups were analysed using χ^2 tests, while demographic differences were assessed using t tests.

2) the main clinical features differentiating the new clinical phenotypes in pathologically-confirmed cases – differences in the prevalence of clinical features between FTD syndromes were analysed using χ^2 tests.

3) the impact of the new clinical criteria on previous clinical diagnoses – differences between new and previous clinical diagnoses were analysed using κ statistics.

4) identification of clinicopathological correlations using the new clinical and pathological criteria - differences in the prevalence of pathological subtype between FTD syndromes were analysed using χ^2 tests, with pathological subgroups with <3 cases omitted from the analysis.

5) differentiating features between FTLD and AD cases - differences in clinical features between pathological diagnoses analysed using discriminate statistics.

All statistical analyses were performed using SPSS (IBM SPSS statistics version 21; SPSS Inc, Chicago, Illinois) and a p value of <0.05 taken as significant.

Supplementary Results

Additional characterization of the clinical cohorts

90% of Cambridge cases versus 55% of Sydney cases had sufficient medical, neurological and neuropsychological assessments required for inclusion in this study with little difference in case demographics between cohorts (Supplementary Table e1). Neuropsychological assessment was instigated in Sydney later than in Cambridge. While there were similar numbers of bvFTD cases in both cohorts, significantly more language variant FTD cases were

available from the Cambridge clinic over the time frame, reflecting referrals to JH over this period. For the combined cohort about 50% had bvFTD and 50% had language variants, reflecting approximate frequencies documented in other large scale clincopathological studies [5, 6].

Additional new clinicopathological correlations

When analysed according to the distribution of clinical subtypes by pathological group, most FTLD-tau cases had bvFTD (64%). A similar proportion of sv-PPA cases had FTLD-tau to those with nfa-PPA. This unexpected result occurred as there was nearly twice as many sv-PPA cases overall compared with nfa-PPA cases, despite sv-PPA having a lower proportion of FTLD-tau cases compared with nfa-PPA. FTLD-TDP cases were split evenly between bvFTD and sv-PPA subtypes (45-43%, Supplementary Table e2) with only a few cases of nfa-PPA and lv-PPA having FTLD-TDP pathology. All FTLD-FUS, FTLD-UPS and FTLD-ni had bvFTD (Supplementary Table e2) with FTLD-FUS cases having significantly younger age at symptom onset ($p<0.0001$), diagnosis ($p<0.0001$) and death ($p<0.0001$), in line with previously observed data [7]. Analysis of clinical symptoms that distinguish pathological subgroups of bvFTD revealed that executive dysfunction, parkinsonism and delusions were more common among cases with FTLD-TDP compared to FTLD-tau (Supplementary Table e3).

While lv-PPA cases made up just over 50% of cases with AD pathology, all other clinical subtypes made up the remainder of cases with pathological AD (Supplementary Table e2) with no significant difference in demographics between pathological AD and the main FTLD subtypes (Supplementary Table e2).

Supplementary Tables

Supplementary Table e1. Demographics and case types ascertained in the different clinic centers.

	Cambridge (N= 96)	**Sydney (N=39)**	***P* Value**	**Combined (N=135)**
% Male/% Female	70/30	56/44	.16	71/29
Age at symptom onset (y)	60 (8)	59 (11)	.65	60 (9)
Age at diagnosis (y)	64 (8)	63 (11)	.47	64 (9)
Age at death (y)	70 (8)	68 (12)	.53	69 (9)
No. of bvFTD (%)	34 (35)	32 (82)	*	66 (49)
No. of sv-PPA (%)	28 (29)	3 (8)	*	31 (23)
No. of nfa-PPA (%)	15 (16)	1 (3)	*	16 (12)
No. of lv-PPA (%)	19 (20)	3 (8)	*	22 (16)

*χ^2 test for difference in frequencies of FTD types between cohorts indicates a significant difference, $p<0.0001$

Supplementary Table e2. Different molecular pathological subtypes observed for the new FTD clinical phenotypes.

	FTLD-tau (N=42)	**FTLD-TDP (N=48)**	**FTLD-FUS (N=8)**	**FTLD-other (N=4)**	**AD (N=33)**
% Male/% Female	64/36	63/37	63/37	75/25	73/27
Age at onset (y)	60 (8)	59 (8)	48 (11)*	60 (7)	64 (10)
Age at diagnosis (y)	64 (7)	63 (7)	50 (10)*	64 (7)	68 (9)
Age at death (y)	69 (8)	69 (9)	55 (10)*	70 (10)	74 (8)
Duration from onset (y)	10 (4)	10 (5)	7 (3)	10 (5)	10 (6)
Duration from diagnosis (y)	5 (3)	6 (4)	5 (2)	6 (5)	6 (3)
No. of bvFTD (%)	27 (64)	19 (43)	8 (100)	4 (100)	6 (18)
No. of sv-PPA (%)	5 (12)	21 (44)	0	0	5 (15)
No. of nfa-PPA (%)	8 (19)	4 (8)	0	0	5 (15)
No. of lv-PPA (%)	2 (5)	2 (5)	0	0	17 (52)

FTLD-other: FTLD-UPS and FTLD-ni. Note: 2 cases were omitted from clinicopathological analysis due to insufficient neuropathological information for a revised diagnosis. *t-test for difference in demographics of FTLD types between cohorts indicates a significant difference, $p<0.0001$

Supplementary Table e3. Symptoms presenting in clinical bvFTD with significantly different prevalances across pathologic groups ($p<0.05$)

	FTLD-tau (N=27)	**FTLD-TDP (N=19)**	**FTLD-FUS (N=8)**	**AD (N=6)**	**p value**
Executive deficits	**41**	74	75	83	0.05
Delusions	**4**	21	**0**	50	0.01
Parkinsonism	**4**	56	25	50	0.03

References for Supplementary Information

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