Journal of Alzheimer's Disease 36 (2013) 49–55
DOI 10.3233/JAD-121969
IOS Press

Overlap between Frontotemporal Dementia and Alzheimer's Disease: Cerebrospinal Fluid Pattern and Neuroimaging Study

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Handling Associate Editor: Amalia Bruni

Accepted 1 March 2013

Abstract.
Background: Differential diagnosis between frontotemporal dementia (FTD) and Alzheimer's disease (AD) is often challenging. Autopsy series have identified AD pathology in a consistent percentage of patients clinically diagnosed with frontotemporal dementia (FTD). It has been demonstrated that the levels of tau and $A\beta_{42}$ in cerebrospinal fluid (CSF) are a reliable marker for AD.
Objective: To evaluate the presence of a CSF AD-like pattern in patients with FTD, and the related brain changes, to assess whether these patients had features resembling an AD pattern of hypoperfusion.
Methods: Clinically-diagnosed non-monogenic FTD patients underwent an extensive neuropsychological assessment, ^{99m}Tc-ECD SPECT, and CSF analysis (tau and $A\beta_{42}$ levels). FTD AD-like and FTD non-AD-like patterns were identified, and neuropsychological and neuroimaging features compared.
Results: CSF AD-like pattern was reported in 9 cases out of 43 (21%). FTD AD-like and non-AD-like patients did not differ in demographic characteristics, cognitive deficits, or behavioral changes. Both groups had greater hypoperfusion in frontotemporal lobes as compared to age-matched controls. When FTD AD-like patients were compared to the FTD non-AD-like group, the former had greater hypoperfusion in brain areas typically affected by AD, namely precuneus, temporal, and parietal areas.
Conclusions: CSF AD-like profile in FTD is associated with brain abnormalities typically found in classical AD, confirming the usefulness of CSF testing. Detecting an ongoing AD pathological process in FTD has several implications for defining distinctive treatment approaches, guiding genetic screening, and helping in patient selection in future clinical trials in both FTLD and AD therapeutics.

Keywords: Alzheimer's disease, amyloid-β, cerebrospinal fluid, frontotemporal dementia, SPECT, tau

INTRODUCTION

Frontotemporal Dementia (FTD) is a clinical heterogeneous disorder characterized by behavioral changes, executive dysfunctions, and language impairment [1–4], with an overall prevalence higher than previously believed [5, 6].

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ISSN 1387-2877/13/$27.50

Even though recent revised criteria have allowed a significant improvement of clinical classification [7, 8] and a more careful description of the selective frontotemporal atrophy [4], in many cases differential diagnosis with other neurodegenerative disorders, i.e., Alzheimer's disease (AD), is still challenging.

The classical picture of AD is indeed different, as defined by memory impairment along with posterior cingulate and parieto-temporal involvement [9, 10]. Notwithstanding, presenile AD patients may present symptoms overlapping with FTD [11, 12] along with primarily frontotemporal damage [13]. On the other hand, autopsy studies have demonstrated that FTD might clinically present severe and isolate amnesia, being indistinguishable from AD in life [14–16]. Further, in neuropathological-proven FTD, it has been reported that elderly patients had more prominent memory deficits than young-onset patients, thus being easily confused with AD [17].

The clinical overlap between these two neurodegenerative disorders has been further accomplished by neuropathological data, demonstrating that AD pathology can be found in 5% to 25% of patients with a clinical diagnosis of FTD [2, 18, 19].

All the above observations highlight the need for biological markers on clinical grounds, to detect the underlined neuropathology, irrespective from clinical and neuroimaging features. This is mandatory for defining different therapeutic approaches, prognosis, genetic screening, and for correct subject recruitment in clinical trials.

Even though no specific reliable biomarker for FTD has been developed yet [20], cerebrospinal fluid (CSF) tau and amyloid-β (Aβ) levels (i.e., high tau and low $A\beta_{42}$ levels) clearly mirror AD pathology [21–23]. Indeed, CSF tau/$A\beta_{42}$ ratio might identify AD at early disease stages [24, 25], even in those cases with atypical presentation [26, 27]. In clinical series with neuropathology confirmation, this CSF ratio has been used to predict the diagnosis of either AD or FTD in typical cases even in the presence of possible copathology [23, 28]. Thus, it might be hypothesized that CSF tau/$A\beta_{42}$ measurement might be useful in detecting atypical AD cases [23] in clinically-diagnosed FTD patients. In the present work, we considered a cohort of patients clinically diagnosed with FTD and with frontotemporal hypoperfusion at single subject analysis, and we assessed levels of CSF tau and $A\beta_{42}$. We aimed to evaluate: 1) the prevalence of a CSF AD-like pattern in patients with clinical FTD; and 2) the brain correlates of patients with CSF AD-like as compared to non-AD-like (nAD-like) patterns, to assess whether the former group had features resembling an AD pattern of hypoperfusion [9, 10].

METHODS

Subjects

Consecutive patients fulfilling current clinical criteria for FTD [7, 8] were recruited from the Centre for Ageing Brain and Neurodegenerative Disorders, University of Brescia, Italy. Only patients with both CSF analysis and single photon emission computed tomography (SPECT) imaging available were considered in the present study.

Each patient underwent a physical evaluation, a routine laboratory examination, and a brain structural imaging study. The diagnostic assessment involved a review of full medical history, a semi-structured neurological examination, and a complete mental status evaluation by at least two independent and experienced reviewers. A standardized cognitive and behavioral assessment was carried out, as previously published [29]. Patients were screened for the most common monogenic forms, namely granulin (*GRN*), microtuble associated protein tau (*MAPT*), and *C9orf72* hexanucleotyde expansion, and genotyped for *APOE* allelic variations, as already reported [30].

Stringent exclusion criteria were applied as follows: 1) cerebrovascular disorders, previous stroke, hydrocephalus, and intra-cranial mass documented by MRI; 2) a history of traumatic brain injury or another neurological disease; 3) significant medical problems including hepatic or renal failure, chronic respiratory insufficiency potentially responsible for encephalopathy; or 4) major depressive disorder, bipolar disorder, schizophrenia, or substance abuse disorder. We excluded cases with a diagnosis of logopenic progressive aphasia, as this was most associated with AD neuropathology [31]. We also excluded cases with the monogenic form of FTD, all associated with an nAD-like CSF pattern.

The work was conformed to the Helsinki Declaration and was approved by local Ethic Committee of Brescia, Italy.

CSF analyses

Lumbar puncture was performed according to a standardized protocol, in the outpatient clinic, from 09 : 30 to 10 : 30, after informed written consent had been obtained. CSF was collected in sterile polypropylene tubes and gently mixed to avoid gradient effects.

Routine chemical measures were determined. The remaining CSF was centrifuged for 3 min at 3000 rpm, and aliquots were stored at −80°C or in liquid nitrogen for subsequent total tau, phospho-tau, and $A\beta_{42}$ measurements. CSF concentrations were measured in duplicate by an ELISA test (Innotest Tau antigen kit and Innotest PHOSHO-TAU 181P; Innogenetics, Ghent, Belgium). Interassay variability was less than 7%. According to our laboratory standards, the cut-off value for total tau is <400 pg/ml and for $A\beta_{42}$ >400 pg/ml. The AD pattern was defined by high total tau levels and low $A\beta_{42}$ levels in CSF, as previously reported by other authors [23].

^{99m}*Tc-bicisate (ECD) SPECT acquisition protocol and image analysis*

Patients were administered an intravenous injection of 1110 MBq of ^{99m}Tc-bicisate (ECD) (Neurolite, Lantheus Medical Imaging) while resting, lying supine in a quiet, dimly lit room. All individuals were imaged using a dual-head rotating gamma camera (GE Millenium VG) fitted with a low-energy, high-resolution collimator, 30 min after intravenous injection of ^{99m}Tc-bicisate (ECD). A 128 × 128 pixel matrix was used for images acquisition with 120 views over a 360° orbit (in 3° step) with a pixel size of 4.02 mm, in 27 min or more to collect at least 5×10^6 total counts. Images reconstruction were performed by a filtered back projection and three-dimensionally smoothed with a Butterworth filter (cut off 0.5 cycles/cm, order 15). The reconstructed images were corrected for gamma ray attenuation using the Chang method (attenuation coefficient: 0.11 cm^{-1}). Statistical Parametric Mapping (SPM8, Welcome Department of Cognitive Neurology, University College, London), and Matlab 7.6 (Mathworks Inc., Sherborn, MA) were used for images pre-processing. Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, MNI) and smoothed by a Gaussian kernel of 8 × 8 × 8 mm FWHM. FTD patients were grouped according to CSF pattern (AD-like and nAD-like), and the following group comparisons were carried out: i) FTLD nAD-like group versus controls, ii) FTD AD-like versus controls, to confirm comparable hypoperfusion patterns in the two patients' groups, and iii) FTD AD-like versus FTD nAD-like, to investigate perfusion differences. Age and gender were considered as nuisance variables. An uncorrected threshold of $p < 0.001$ were used for whole brain analysis, with a minimum cluster threshold set at 100 voxels.

Statistical analysis

Results are expressed as mean ± standard deviation. Chi-Square or Mann-Whitney test were used, as appropriate. In regards to neuropsychological scores, the statistical significance for multiple testing was $p < 0.001$ (corrected for Bonferroni's *post-hoc* test). Data analyses were carried out using SPSS 16.0 software (Chicago, USA).

RESULTS

Subjects

43 FTD patients were included in the study. Thirty-one were diagnosed with behavioral variant frontotemporal dementia (bvFTD), 6 with agrammatic variant of primary progressive aphasia (avPPA), and 6 with semantic variant of PPA (svPPA). Mean age at onset was 62.1 ± 7.01 years, 58.1% were female, and 36.6% were *APOE* ε4 carriers. In the overall group, mean CSF $A\beta_{42}$ levels were within the normal range whereas CSF tau levels were slightly increased (see Table 1).

According to CSF data, 9 (21%) FTD AD-like and 34 nAD-like (79%) patients were identified. As reported in Table 1, FTD AD-like and FTD nAD-like were comparable in term of demographic characteristics, except for family history (0% versus 23.5%, $p = 0.04$). *APOE* genotype distribution was similar within groups. In the group of AD-like FTD cases, six were clinically classified as bvFTD, two as avPPA, and one as svPPA. The neuropsychological, behavioral, and motor assessment of FTD AD-like and FTD nAD-like patients is shown in Table 2. At the pre-established threshold ($p < 0.001$), no differences in neuropsychological testing or behavioral scores in AD-like and nAD-like patients were reported.

Imaging analysis

As shown in Fig. 1, when either AD-like or nAD-like patients were compared to a group of age-matched healthy controls, significant greater hypoperfusion of frontotemporal regions was detected in both groups. Furthermore, sorting for clinical diagnosis, a coherent pattern of hypoperfusion was evident for the three subgroups (bvFTD: bilateral prefrontal hypoperfusion avPPA: left fronto-insular hypoperfusion; svPPA: left predominant anterior temporal hypoperfusion), further supporting the clinical diagnosis of FTD (data not shown).

Table 1
Demographic and clinical characteristics according to CSF pattern in FTD patients

Variable	FTD all ($n=43$)	nAD-like ($n=34$)	AD-like ($n=9$)	Control group ($n=14$)	p
Age at evaluation, years	64.3 ± 7.1	61.6 ± 6.8	65.3 ± 8.5	63.0 ± 7.6	0.30
Gender, F %	58.1	55.9	66.7	41.7	0.56
Positive family history, %	18.6%	23.5%	0%		0.04
Age at onset, years	62.1 ± 7.1	61.6 ± 6.8	63.6 ± 8.5		0.77
Education, years	7.1 ± 3.0	6.8 ± 3.0	8.1 ± 3.1		0.11
bvFTD/avPPA/svPPA (n)	31/6/6	25/5/4	6/2/1		0.75
APOE ε4 %	36.6	40.6	22.2		0.31
FTD-CDR global score	4.6 ± 2.9	4.2 ± 2.8	6.1 ± 3.1		0.07
CSF tau, pg/ml	506.0 ± 340.0	417.1 ± 283.4	842.8 ± 338.1		<0.001
CSF $A\beta_{42}$, pg/ml	731.3 ± 430.4	836.3 ± 423.1	334.4 ± 75.1		<0.001
CSF p-tau, pg/ml	84.8 ± 89.4	67.4 ± 72.4	150.6 ± 120.8		0.02

FTD, frontotemporal dementia; AD, Alzheimer's disease; nAD-like, non-Alzheimer's disease-like; bvFTD, behavioral variant frontotemporal dementia; avPPA, agramatic variant of primary progressive aphasia; svPPA, semantic variant of PPA; *APOE*, apolipoprotein E; FTD-CDR, frontotemporal dementia-modified Clinical Dementia Rating scale; CSF, cerebrospinal fluid.

Table 2
Neuropsychological, behavioral, and motor assessment according to CSF pattern

Variable	FTD	nAD-like	AD-like	p
MMSE	22.5 ± 5.4	23.4 ± 4.6	18.8 ± 7.4	0.08
UPDRS-III	7.8 ± 8.9	8.9 ± 9.5	3.3 ± 3.55	0.27
Short story	5.6 ± 4.1	6.1 ± 3.9	3.5 ± 4.1	0.12
Raven matrices	20.7 ± 5.8	21.3 ± 6.1	17.8 ± 2.8	0.15
Rey figure, copy	23.9 ± 8.9	24.6 ± 8.1	20.1 ± 12.1	0.40
Rey figure, recall	7.8 ± 7.0	7.8 ± 6.8	7.8 ± 8.5	0.64
Phonological fluency	16.4 ± 11.8	17.0 ± 12.2	13.7 ± 10.0	0.52
Semantic fluency	21.6 ± 11.6	22.8 ± 11.9	16.0 ± 8.8	0.19
Digit span, backward	4.5 ± 1.1	4.5 ± 1.1	4.4 ± 1.0	0.86
Token test	27.3 ± 6.8	27.4 ± 7.3	26.9 ± 4.4	0.48
Trail making, A	172.4 ± 161.6	154.5 ± 155.7	249.5 ± 175.8	0.03
Trail making, B	340.7 ± 162.0	315.7 ± 166.7	456.0 ± 62.4	0.10
Clock's drawing	5.6 ± 2.7	6.0 ± 2.6	3.8 ± 1.6	0.08
NPI	15.8 ± 11.8	16.2 ± 12.3	14.6 ± 10.7	0.91
FBI AB	14.5 ± 9.7	14.4 ± 10.1	15.0 ± 8.8	0.85
FBI A	10.5 ± 6.2	10.3 ± 6.2	11.0 ± 6.3	0.52
FBI B	4.2 ± 4.1	4.2 ± 4.3	4.0 ± 3.6	0.98

FTD, frontotemporal dementia; AD, Alzheimer's disease; nAD-like: non-Alzheimer's disease-like; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; NPI, Neuropsychiatry Inventory; FBI, Frontal Behavioral Inventory.

Thus, in FTD AD-like patients significant greater hypoperfusion of superior temporal lobe (2866 voxels, −52, −60, 18; P FWE-cluster level <0.05, $T=4.96$), precuneus (470 voxels, −6; −48; 48; $p<0.001$ $T=4.53$, not surviving FWE correction), and right inferior parietal lobe (298 voxels, 52, −44, 22; $p<0.0001$, $T=4.76$, not surviving FWE correction) was observed, as compared to nAD-like patients (see Fig. 2). The opposite comparison, i.e., nAD-like < AD-like, did not show any significant result at the pre-established threshold.

An exploratory single subject analysis was further performed in FTD AD-like patients to corroborate the present findings. When each FTD AD-like patient was compared to the control group, frontotemporal hypoperfusion pattern, in some cases involving parietal lobe, was observed (see Supplementary Figure 1; available online: http://dx.doi.org/10.3233/JAD-121969).

DISCUSSION

In the last ten years, it has been widely demonstrated that CSF $A\beta_{42}$ and tau levels are reliable biomarkers for the diagnosis of AD, even in patients with subtle cognitive disorders and in those subjects with clinical diagnosis of other neurodegenerative dementias [25, 26]. Further, autopsy data have reported that CSF tau/$A\beta_{42}$ measurements show a strong correlation with AD-related Aβ senile plaque pathology [32–34]. In this view, CSF biomarkers have recently been added to the clinical diagnostic criteria for AD [25, 35].

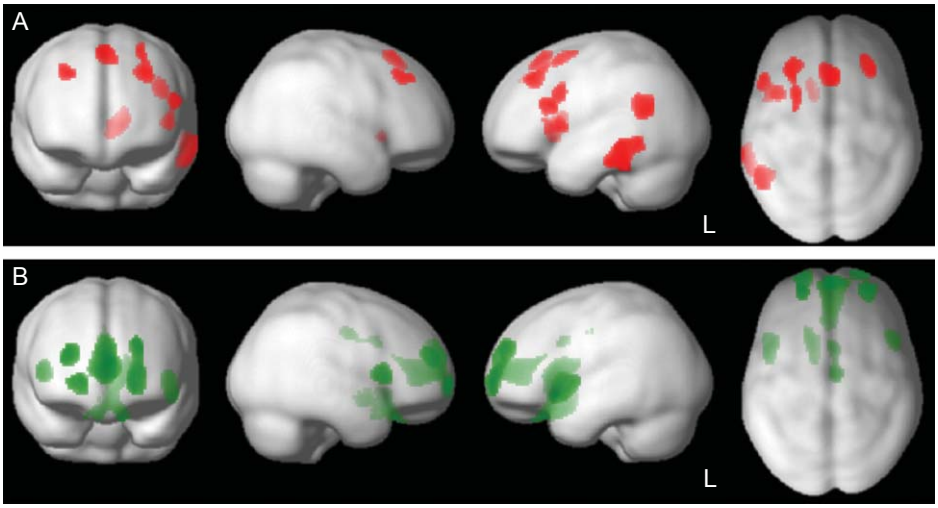

Fig. 1. Results of group comparisons superimposed on a 3D brain template. A) FTD nAD-like group versus healthy controls. B) FTD AD-like group versus healthy controls. $p < 0.001$ uncorrected, threshold = 100 voxels. L = left.

Fig. 2. Comparison between FTD AD-like group and FTD nAD-like group, superimposed on T1-weighted RMN slices. $p < 0.001$ uncorrected, threshold = 100 voxels.

We found that 21% of patients fulfilling current clinical criteria of FTD [7] had a CSF AD-like pattern. When AD-like patients were compared to those with CSF tau/Aβ_{42} within normal range, significant hypoperfusion in precuneus, parietal, and temporal lobes was reported.

As demonstrated by a wide body of literature, the involvement of these regions is specifically suggestive of AD pathology [4, 9, 11, 36]. For that, we might argue that FTD patients with CSF AD-like pattern are instead cases with atypical and focal AD pathology [11]. The percentage of patients reclassified by CSF analysis (21%) is indeed in line with several previous pathological series [19, 37].

Alternatively, we cannot even exclude that CSF and neuroimaging AD-like changes may herald and co-occur in patients with FTLD [23]. A recent work has highlighted how neurodegenerative diseases may coexist, and in the analyzed samples, almost 25% of the cases presented multiple neurodegenerative pathologies [38]. Even in some genetic cases linked to *C9orf72* expansion, there is evidence of AD and TDP-43 co-pathology [39, 40], underlying the importance of a fully extended genetic screening in FTD patients.

In both cases, patients with clinical FTD but with AD pathological hallmarks deserve different therapeutic approaches and should be considered differently in future clinical trials of either FTLD or AD treatments. In presence of FTD CSF-AD-like pattern, a genetic *PSEN1* or *PSEN2* screening should be considered to exclude rare monogenic AD-variant.

If a high CSF tau/Aβ ratio is highly specific for AD, in FTLD, no specific CSF pattern has been found yet [20, 41]. In FTLD, Aβ_{42} levels are within normal range and tau levels usually present spread values [23]. However, as stated in the new revised crite-

ria validated for bvFTD, biomarkers indicative of AD are considered an exclusion criterion (even without a conclusive role of either CSF or PET PiB scan). The present work confirms and further extents this statement, demonstrating that patients with CSF AD-like pattern have specific features, resembling AD changes at neuroimaging evaluation.

We acknowledge that this work has several limitations. Firstly, neuropathological confirmation and the combined use of Aβ tracers would be mandatory to definitively clarify the present findings [42]. Secondly, a more careful neuropsychological assessment might be of help for further differentiating AD-like and nAD-like subgroups. Finally, follow-up of these patients might be interesting to evaluate different trajectories of progression.

In conclusion, we suggest that CSF tau/Aβ analysis should be considered as a surrogate marker of underlying AD pathology *in vivo* in FTD cases.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1700).

SUPPLEMENTARY MATERIAL

Supplementary material can be found here: http://dx.doi.org/10.3233/JAD-121969

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