

Frontal presentation of Alzheimer's disease

A series of patients with biological evidence by CSF biomarkers

Leonardo Cruz de Souza¹, Maxime Bertoux¹, Aurélie Funkiewiez², Dalila Samri², Carole Azuar¹, Marie-Odile Habert³, Aurélie Kas³, Foudil Lamari⁴, Marie Sarazin¹, Bruno Dubois¹

ABSTRACT. Besides its typical amnesic presentation, focal atypical presentations of Alzheimer's disease (AD) have been described in neuropathological studies. These phenotypical variants of AD (so-called "atypical AD") do not follow the typical amnesic pattern and include non-amnesic focal cortical syndromes, such as posterior cortical atrophy and frontal variant AD. These variants exhibit characteristic histological lesions of Alzheimer pathology at *post-mortem* exam. By using physiopathological markers, such as cerebrospinal fluid markers, it is now possible to establish *in vivo* a biological diagnosis of AD in these focal cortical syndromes. We report a series of eight patients who were diagnosed with behavioural variant frontotemporal dementia based on their clinical, neuropsychological and neuroimaging findings, while CSF biomarkers showed an AD biological profile, thus supporting a diagnosis of frontal variant of AD.

Key words: Alzheimer's disease, frontotemporal dementia, CSF biomarkers.

APRESENTAÇÃO FRONTAL DA DOENÇA DE ALZHEIMER: UMA SÉRIE DE PACIENTES COM EVIDÊNCIA BIOLÓGICA POR BIOMARCADORES NO LCR

RESUMO. Além da típica forma amnésica, apresentações focais atípicas da doença de Alzheimer (DA) foram descritas em estudos anatomopatológicos. Essas variantes fenotípicas da DA ("DA atípica") não seguem o padrão amnésico convencional e incluem síndromes corticais focais não amnésicas, tais como a atrofia cortical posterior e a variante frontal da DA. Essas variantes apresentam lesões histológicas características da DA ao exame patológico *post-mortem*. O uso de marcadores fisiopatológicos da DA, como os biomarcadores do líquido cefalorraquidiano, permite estabelecer *in vivo* um diagnóstico biológico de DA nessas síndromes corticais focais. Reportamos uma série de oito pacientes que foram clinicamente diagnosticados como portadores da variante comportamental da demência frontotemporal (de acordo com critérios clínicos, neuropsicológicos e de neuroimagem), mas nos quais a investigação dos biomarcadores do líquido mostrou um perfil biológico de DA, de modo que o diagnóstico da variante frontal de DA foi finalmente estabelecido.

Palavras-chave: doença de Alzheimer, demência frontotemporal, biomarcadores do líquido.

INTRODUCTION

Alzheimer's disease (AD) has been classically defined as a progressive amnesic neurodegenerative disorder with subsequent emergence of other cognitive and neuropsychiatric changes that impair activities of daily living.¹ In typical presentations, patients with AD manifest early episodic memory deficit

followed by various associations with executive, language and visuospatial deficits. The identification of this specific clinical and cognitive profile has been the core of the clinical diagnosis of AD, as established by the NINCDS-ADRDA criteria.²

In contrast to this typical amnesic profile, focal atypical presentations of AD have been

¹Université Pierre et Marie Curie Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle Epinière, UMR-S975, 47-83 bd de l'Hôpital, 75013 Paris, France. Inserm, U975, 47-83 bd de l'Hôpital, 75013 Paris, France. CNRS, UMR 7225, 47-83 bd de l'Hôpital, 75013 Paris, France. ²Institut du Cerveau et de la Moelle Epinière, ICM, 47-83 bd de l'Hôpital, 75013 Paris, France. Alzheimer Institute; Research and Resource Memory Centre; Centre de Référence des Démences Rares, Centre de Référence Maladie d'Alzheimer jeune, AP-HP, Pitié-Salpêtrière Hospital, 47-83 boulevard de l'Hôpital, 75013 Paris, France. ³Université Pierre et Marie Curie Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle Epinière, UMR-S975, 47-83 bd de l'Hôpital, 75013 Paris, France. Alzheimer Institute; Research and Resource Memory Centre; Centre de Référence des Démences Rares, Centre de Référence Maladie d'Alzheimer jeune, AP-HP, Pitié-Salpêtrière Hospital, 47-83 boulevard de l'Hôpital, 75013 Paris, France. ⁴Service de Médecine Nucléaire, AP-HP, Groupe hospitalier Pitié-Salpêtrière, F-75013, Paris, France. ⁵Department of Metabolic Biochemistry, Pitié-Salpêtrière Hospital, Paris, France.

Leonardo Cruz de Souza. Alzheimer Institute; Research and Resource Memory Centre; Centre de Référence des Démences Rares, Centre de Référence Maladie d'Alzheimer jeune, AP-HP, Pitié-Salpêtrière Hospital, 47-83 boulevard de l'Hôpital – 75013 Paris – France. E-mail : leocruzsouza@hotmail.com

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described in neuropathological studies.³⁻⁶ These phenotypic variants of AD (so-called “atypical AD”)⁷ do not follow the typical amnesic pattern and include non-amnesic focal cortical syndromes, such as posterior cortical atrophy and frontal variant AD. These variants exhibit characteristic histological lesions of Alzheimer pathology at *post-mortem* exam. Alzheimer pathology is indeed the most frequent pathological diagnosis associated with posterior cortical atrophy. By contrast, it is less frequently reported in patients presenting prominent behavioural deficits^{3,5,8,9} such as those observed in the behavioural variant frontotemporal dementia (bvFTD).

With the recent advances in physiopathological markers of AD, the underlying pathological process of AD may be identified *in vivo* in patients who present with an atypical clinical presentation. By using physiopathological markers, such as amyloid markers on neuroimaging and cerebrospinal fluid (CSF) markers, it is now possible to establish *in vivo* a biological diagnosis of AD in these focal cortical syndromes.¹⁰⁻¹²

Here we report a series of eight patients who were diagnosed with bvFTD based on their clinical, neuropsychological and neuroimaging findings, while CSF biomarkers showed an AD biological profile, thus supporting a diagnosis of frontal variant of AD.

METHODS

We searched the database at the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital for patients for whom a diagnosis of bvFTD had been established according to clinical criteria. From this series, we selected those patients with a “CSF AD biomarker profile”. A “CSF AD biomarker profile” was defined as a P-Tau/A β_{42} ratio higher than 0.21, as this distinguishes AD from bvFTD with a high sensitivity (91.2%) and specificity (92.6%).¹¹ All selected patients in this “frontal AD group” fulfilled the revised Lund-Manchester consensus criteria for bvFTD¹³⁻¹⁵ including: [1] a corroborated history of initial progressive decline in social interpersonal conduct and behavioral symptoms such as emotional blunting, apathy, reduced empathy, disinhibition, stereotypic behaviors, alterations in food preference and poor self-care; [2] the presence of dysexecutive difficulties at the neuropsychological exam; [3] anatomical magnetic resonance imaging (MRI) and/or single Photon Emission Computed Tomography (SPECT) disclosing frontal atrophy and/or blood hypoperfusion.

We did not include subjects who presented with the following: [1] clinical or neuroimaging evidence of focal lesions; [2] severe depression; [3] early impairment of praxis and spatial skills; [4] patients with language dis-

orders characteristic either of progressive non-fluent aphasia or semantic aphasia; [5] severe cortical or sub-cortical vascular lesions, and [6] inflammatory, infectious or vascular diseases that could account for cognitive/behavioral impairment.

Clinical and neuropsychological data from patients with frontal AD were compared with three groups of subjects selected from the database of the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital: [i] patients with typical amnesic AD (n=18), with CSF AD biological profile (P-Tau/A β_{42} ratio higher than 0.21); [ii] patients with bvFTD (n=18) that fulfilled the last revised diagnostic criteria for bvFTD¹⁵ and who had normal CSF biomarker profile (P-Tau/A β_{42} ratio lower than 0.21); and [iii] normal controls (n=18) selected according to the following criteria: Mini-Mental State Exam (MMSE) ≥ 27 and normal neuropsychological testing.¹⁶ Subjects from frontal AD, typical amnesic AD and bvFTD groups were matched for educational level and disease duration.

Statistical behavioral analysis. All statistical analyses were performed with the STATISTICA 5.5A software (© StatSoft, Tulsa, Oklahoma, USA). Descriptive statistics were used to characterize each group. The Mann-Whitney test was employed to compare differences in distributions between the “frontal AD” group and each of the other three groups (healthy controls, typical AD and bvFTD groups).

Measurement of CSF biomarkers. CSF samples were collected by lumbar puncture (LP) and analyzed for total Tau, Tau phosphorylated at threonine 181 (P-Tau) and A β_{42} with a double-sandwich enzyme-linked immunosorbent assay (ELISA) method (Innogenetics, Gent, Belgium) at the Metabolic Biochemistry Department of the Pitié-Salpêtrière Hospital, as previously described.¹¹

For all patients, the biological and clinical data were generated during a routine clinical work-up and were retrospectively extracted for this study. According to French legislation, explicit informed consent was waived, as patients and their relatives had been informed that individual data might be used in retrospective clinical research studies.

RESULTS

Eight patients (seven men, one woman) were selected according to the inclusion criteria for “frontal AD”. Demographic, clinical and neuroimaging data for each patient are shown in Table 1, while neuropsychological data are presented in Table 2. The age of patients at

Table 1. Demographic, clinical, neuroimaging and CSF data for each patient.

	AJP	CN	LD	MJJ	MY	PM	RD	TA
Sex	Male	Male	Male	Male	Male	Male	Male	Female
Age at evaluation (years)	68	68	56	72	76	62	57	49
Age at onset (years)	59	62	54	70	73	58	55	48
Family history of AD	No	No	No	No	Yes	No	Yes	No
Behavioral symptoms	Apathy, gluttony, collectionism, obsessions, neglect of personal self-care	Apathy, aggressive behavior, motor stereotypies, indifference, disinhibition	Motor stereotypies, aggressive behaviour, logopenia, anosognosia	Apathy, anosognosia, decline in social interpersonal conduct	Joviality, disinhibition, decline in social interpersonal conduct	Apathy, gluttony, aggressive behaviour, obsessions, neglect of personal self-care, logopenia	Joviality, disinhibition, decline in social interpersonal conduct, anosognosia	Affective indifference, apathy, social withdrawal
Brain MRI	Not performed (normal CT scan)	Global cortical atrophy	Frontal atrophy	Frontal atrophy	Global cortical atrophy	Global cortical atrophy	Global cortical atrophy	Frontal atrophy
SPECT	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion	Marked frontal hypoperfusion
Aβ ₄₂	210	230	186	317	125	167	412	329
Tau	386	357	648	1064	504	1200	1200	1200
P-Tau	76	70	97	138	84.5	159	202	140
Tau/Aβ ₄₂	1.84	1.55	3.48	3.36	4.03	7.19	2.91	3.65
P-Tau/Aβ ₄₂	0.36	0.30	0.52	0.44	0.68	0.95	0.49	0.43

Table 2. Neuropsychological data for each patient.

	AJP	CN	LD	MJJ	MY	PM	RD	TA
MMSE (/30)	16	22	10	19	26	10	17	21
Orientation time/space (/10)	8	10	4	8	10	2	4	8
MATTIS (/144)	121	126	108	77	NA	101	111	121
MATTIS – Attention (/37)	35	36	33	29	NA	36	36	37
MATTIS – Initiation (/37)	35	27	28	13	NA	17	23	28
MATTIS – Construction (/6)	5	6	4	4	NA	5	5	6
MATTIS – Concepts (/39)	30	36	26	12	NA	36	35	31
MATTIS – Memory (/25)	16	21	39	19	NA	7	12	19
Memory: Encoding (FCSRT) (/16)	10	10	3	NA	14	2	9	8
Total Free Recall (FCSRT) (/48)	8	9	NC	NA	13	NC	0	8
Total (Free + Cued) Recall (FCSRT) (/48)	27	18	NC	NA	41	NC	12	14
Verbal Span (Direct – Indirect)	5-3	5-4	4-2	4-2	5-4	4-3	5-4	6-4
Phonemic Fluency in 2 minutes	14	10	3	1	4	3	14	7
Category Fluency in 2 minutes	18	13	3	2	21	5	15	6
FAB (/18)	13	14	5	2	13	7	8	13
Wisconsin (/20)	3	6	NA	3	9	3	NA	9
Mini-SEA	11.7	21.7	NA	NA	18.8	13.5	NA	12.1
Gestural Apraxia	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent

FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; Mini-SEA: Mini version of the Social Cognition and Emotional Assessment; MMSE: Mini-Mental State Exam; NA: Data not available; NC: Not continued (the evaluation of episodic memory was not continued due to severe encoding deficits).

Table 3. Clinical and neuropsychological data between groups.

	Frontal AD (n=8)	Controls (n=18)	AD (n=18)	bvFTD (n=18)
Age at evaluation (years)	63.5 (±8.9)	68.6 (±7) ^{NS}	64.8 (±9.6) ^{NS}	65.7 (±7.9) ^{NS}
Disease duration (years)	3.5 (±2.4)	NA	3.4 (±1.7) ^{NS}	3.2 (±1.6) ^{NS}
Sex (male/female)	7/1	10/8	9/9	9/9
Educational level (in years)	10.4 (±3.9)	12.2 (±2.3) ^{NS}	10.5 (±3.9) ^{NS}	9.8 (±4.3) ^{NS}
MMSE (/30)	17.6 (±5.6)	29.6 (±0.6)*	22.2 (±2.9)**	23.3 (±3.6)**
Orientation time/space (/10)	6.3 (±2.9)	9.4 (±2.3)*	8 (±1.9) ^{NS}	8 (±1.8) ^{NS}
MATTIS (/144)	109.3 (±16.7)	143.3 (±1.5)*	NA	119.2 (±12.3) ^{NS}
MATTIS – Attention (/37)	34.6 (±2.8)	37 (±0)**	NA	33.9 (±3.6) ^{NS}
MATTIS – Initiation (/37)	24.4 (±7.4)	36.5 (±1.0)**	NA	27.4 (±5.6) ^{NS}
MATTIS – Construction (/6)	5 (±0.8)	6 (±0)**	NA	5.6 (±0.7) ^{NS}
MATTIS – Concepts (/39)	29.4 (±8.5)	39 (±0)*	NA	32 (±4.9) ^{NS}
MATTIS – Memory (/25)	19 (±10)	24.8 (±0.5) ^{NS}	NA	19 (±3.7) ^{NS}
Memory: Encoding (FCSRT) (/16)	8 (±4.2)	15.7 (±0.6)*	12.4 (±1.9)*	13.8 (±3)**
Total Free Recall (FCSRT) (/48)	5.4 (±5.3)	33.8 (±7.9)*	12 (±5.3)**	16.9 (±5.2)*
Total (Free + Cued) Recall (FCSRT) (/48)	16 (±14.6)	46 (±1.8)*	30.8 (±8.6)**	39.9 (±7.6)**
Verbal Span (Direct)	4.8 (±0.7)	5.5 (±0.7)**	4.8 (±1.3) ^{NS}	5.2 (±1.4) ^{NS}
Verbal Span (Indirect)	3.3 (±0.09)	4 (±0.6) ^{NS}	3.4 (±1.2) ^{NS}	3.1 (±0.9) ^{NS}
Phonemic Fluency in 2 minutes	7 (±5.1)	13.7 (±3.2)**	8.2 (±6.3) ^{NS}	6.6 (±3.8) ^{NS}
Category Fluency in 2 minutes	10.4 (±7.3)	19.1 (±4.5)**	13.8 (±4.8) ^{NS}	10.6 (±3.9) ^{NS}
FAB (/18)	9.4 (±4.5)	16.9 (±0.9)*	13 (±2.3)**	11.6 (±3.3) ^{NS}
Wisconsin (/20)	6 (±3)	19 (±1.1)*	NA	2.5 (±1.7) ^{NS}
Mini-SEA	24 (±16)	41.2 (±6.9)*	NA	26.2 (±3.4)**

FAB: Frontal Assessment Battery; FCSRT: Free and Cued Selective Reminding Test; Mini-SEA: Mini version of the Social Cognition and Emotional Assessment; MMSE: Mini-Mental State Exam; NA: Data not available. Comparison between frontal variant AD patients and other groups was performed using a non-parametric Mann-Whitney U-test with the following annotations: ^{NS}Non significant vs frontal variant AD group. *p<0.001. **p<0.05

the time of clinical evaluation varied between 49 and 76 years. The age at onset of symptoms varied between 48 and 73 years. No patient had familial antecedents of bvFTD, but there was a family history of AD for two patients (patients “MY” and “RD”). According to inclusion criteria, all frontal AD patients had abnormal P-Tau/A β_{42} ratio. Moreover, all frontal AD patients had reduced A β_{42} (<450 pg/mL) and high P-Tau (>60 pg/mL) levels.

The most frequent behavioral signs among patients with frontal AD were apathy (5 out of 8 patients), obsessive stereotypies (4 out of 8), decline in social interpersonal conduct (3 out of 8), irritability/aggressive behavior (3 out of 8), binge eating (2 out of 8), and neglect of personal self-care (2 out of 8). At the onset of the disease, two patients had predominantly inert behavior presentation; three patients had a disinhibited profile, and three others had a mixed profile.

Scores on the MMSE differed significantly between

frontal AD patients and healthy controls, with lower scores for frontal AD patients (Table 3). All scores on frontal tests were significantly lower in frontal AD patients as compared to healthy controls (Table 3). More specifically, four frontal AD patients had time-space disorientation at neuropsychological exam, while four had good orientation. All frontal AD patients had poor performance on working memory tests (verbal spans). Dysexecutive deficits were present in all patients. Five out of eight frontal AD patients were evaluated with the short version of the Social Cognition and Emotional Assessment (Mini-SEA);¹⁷ all these patients had severe deficits on theory of mind and facial emotion recognition tests. Five out of eight frontal AD patients had episodic memory impairment on the Free and Cued Selective Reminding Test (FCSRT),¹⁸ with the so-called “amnestic syndrome of the medial temporal type” (low free recall not normalized with cueing). Two frontal AD patients had severe encoding deficits that limited the evaluation

of episodic memory by the FCSRT and one patient did not undergo episodic memory evaluation with the FC-SRT. No frontal AD patients presented gestural apraxia.

There was no significant difference between frontal AD and bvFTD groups for MATTIS scores, verbal spans, verbal fluencies (phonemic and category) and for Wisconsin score (Table 3).

As an illustrative example, we report the clinical vignette of one of the patients included in this study. Mrs. TA, a medical nurse aged 48 years, was referred to the Behavioral Unit of the Pitié-Salpêtrière Hospital in April 2010 for marked apathy, affective indifference and social withdrawal which had been evolving for approximately one year. The patient also had a history of reduced verbal output. Her husband did not report memory difficulties or spatial disorientation. The activities of daily living were globally preserved. A previous psychiatric referral led to a diagnosis of depression, and the patient was in use of antidepressants (venlafaxine). Her preceding medical history was unremarkable. There was no history of hallucinations, head trauma, neuroleptic medications, or alcohol/drug abuse. There was no family history of neurological diseases or dementia. The standard neurological examination was normal, without abnormalities of eye movement. She had no motor signs, no extrapyramidal syndrome, and no myoclonus.

Neuropsychological tests showed an impairment in global cognitive efficiency (MMSE 21/30 and MATTIS scale 121/144), without disorientation in time and space. The patient presented a severe dysexecutive syndrome, with attentional and working memory deficits. Mental flexibility and the abilities of conceptualizing and programming were severely impaired on the Trail Making Test (TMT),¹⁹ on the modified Wisconsin Card Sorting Test²⁰ and on the copy of Rey complex figure.²¹ The patient had impaired performance on tests of theory of mind and of facial emotion recognition (mini-SEA). There was an episodic memory deficit characterized by a low free recall (free recall score=8/48) not normalized with cueing (total recall=14/48). The patient had no deficits on the execution of gestures from the limb apraxia battery.²² There were no signs of Bálint or Gertsmann syndromes.

Language assessment demonstrated that there was no reading or writing impairment, with preserved written language comprehension. Verbal fluencies were reduced, both in phonemic (only four “p” words in two minutes) and categorical modalities (only nine fruits in two minutes), with slight difficulty on the denomination task (74/80). There was no speech apraxia and no semantic deficit.

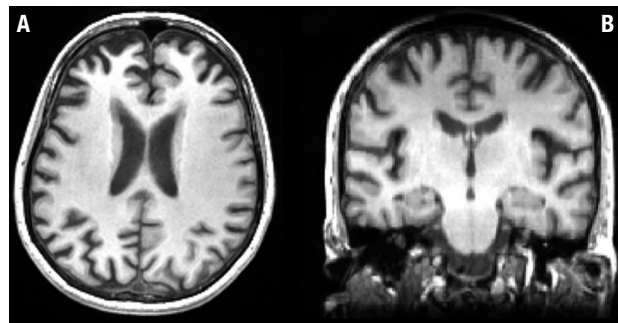


Figure 1. Brain MRI from patient TA, 48 year-old woman. [A] Axial slice: mild cortical frontal atrophy, predominant in medial regions. [B] Coronal slice: absence of hippocampal atrophy.

Brain MRI (Figure 1) revealed mild cortical frontal atrophy, without medial temporal atrophy. Brain SPECT (Figure 2A) showed moderate hypoperfusion in medial and dorsolateral prefrontal cortex, with left predominance. There was very mild hypoperfusion in the left parietal cortex. Cerebral perfusion was preserved in medial temporal regions.

The patient underwent a complete blood and CSF exam in order to exclude other causes of non-neurodegenerative dementia in young patients (autoimmune diseases, paraneoplastic pathology, CNS infection, metabolic diseases, and so on). These exams were all negative.

The diagnosis of bvFTD was initially established on a clinical basis by the neurologist (BD), as the clinical picture fulfilled the criteria for the disease: [1] a corroborated history of initial progressive decline in social interpersonal conduct, with apathy, affective indifference and loss of empathy; [2] the presence of severe difficulties in executive and social-emotional abilities; [3] atrophy of frontal lobes on brain MRI and marked hypoperfusion of frontal lobes on SPECT, with preservation of medial temporal and parietal regions. Taking into account these clinical data, the presence of significant amnesia was not considered incompatible with the diagnosis of bvFTD.

However, some weeks after hospitalization, data on CSF biomarkers were available and showed low $A\beta_{42}$ (329 pg/mL), high Tau (1200 pg/mL) and high P-Tau (140 pg/mL), in favor of an AD diagnosis. All derived ratios (Tau/ $A\beta_{42}$ and P-Tau/ $A\beta_{42}$) were also in favor of AD. Considering these results, a diagnosis of frontal variant of AD was proposed.

On the clinical follow-up over 30 months, there was a marked deterioration in cognitive abilities and the patient manifested disorientation in time and space as well as limb apraxia and presented an aggravation of both

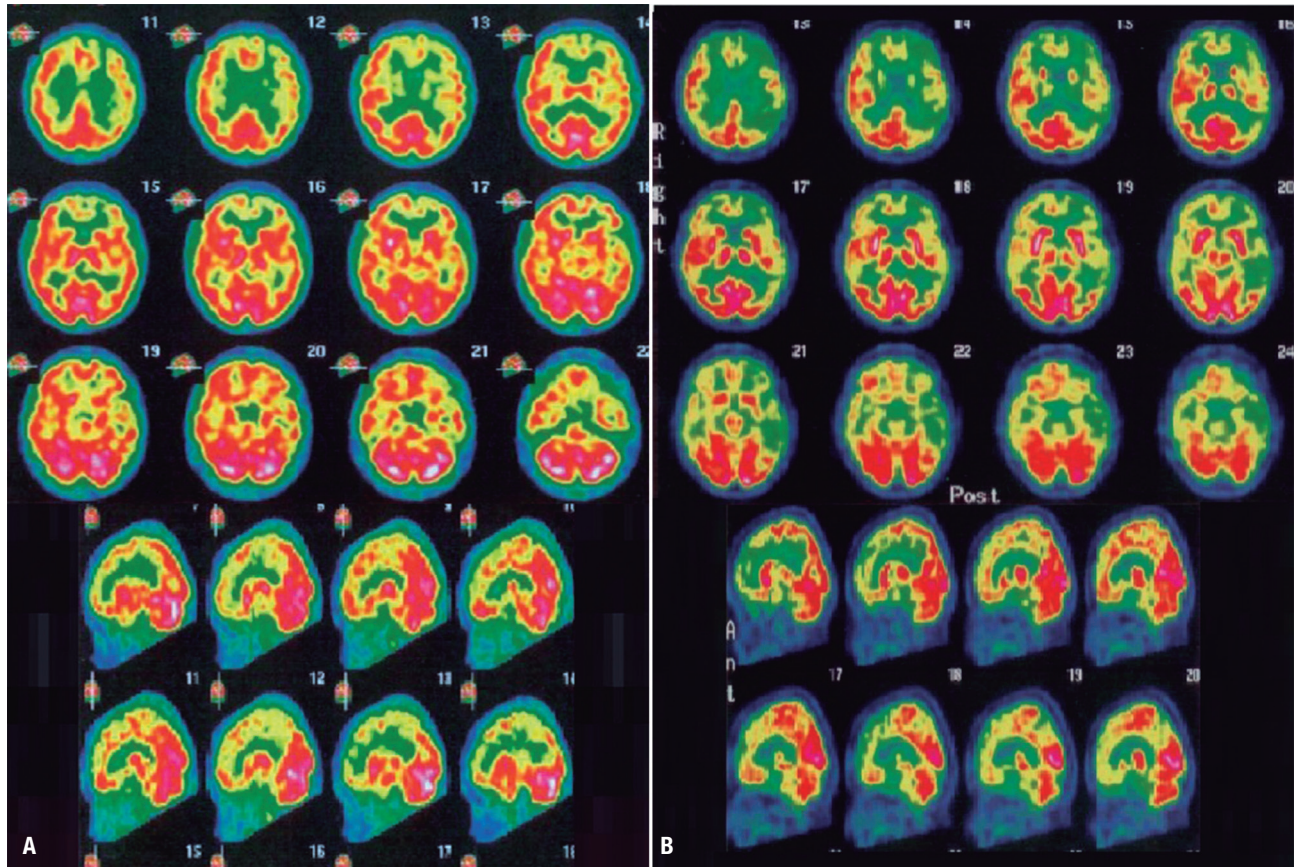


Figure 2. Brain scintigraphy (SPECT) from patient TA, 48 year-old woman. [A] Brain SPECT after approximately one year since symptoms onset (May/2010): moderate hypoperfusion in medial and dorsolateral prefrontal cortex, with left predominance; very mild hypoperfusion in the left parietal cortex; no hypoperfusion in medial temporal regions. [B] Brain SPECT approximately two years after symptoms onset (March/2011): severe hypoperfusion in prefrontal cortex (with left predominance); severe hypoperfusion in the left parieto-temporal cortex; mild hypoperfusion in the right parieto-temporal cortex; very mild hypoperfusion in the medial temporal regions.

amnesia and dysexecutive deficits. The patient clinically progressed to multi-domain cognitive impairment, with loss of autonomy, thus defining the dementia stage of the disease. The patient underwent another brain SPECT exam (Figure 2B) which showed severe hypoperfusion in prefrontal cortex (with left predominance), severe hypoperfusion in the left parieto-temporal cortex and mild hypoperfusion in the right parieto-temporal cortex. There was very mild hypoperfusion in the medial temporal regions. The patient has been treated with antidepressants and with an anticholinesterasic. She was also included in a clinical immunotherapy trial.

DISCUSSION

We reported a series of eight patients which fulfilled clinical consensual criteria for bvFTD, but for whom a diagnosis of frontal variant AD was finally proposed on the basis of CSF biomarkers. Previous studies with either biological,²³ genetic²⁴ or pathological confirma-

tion^{3,5,8,25,26} have also reported focal atypical presentations of AD mimicking bvFTD.

FTD is the second most frequent cause of degenerative dementia in patients below 65 years old²⁷ and includes three clinical subtypes: the behavioral variant (bvFTD) and the language variants, progressive non-fluent aphasia and semantic aphasia.^{27,28}

bvFTD is the most common presentation of FTD²⁹ and is clinically characterized by an insidious and gradually progressive behavioral syndrome defined by a decline in social interpersonal conduct, impairment in regulation of personal conduct, emotional blunting and a loss of insight.¹⁴ bvFTD is typically associated with frontal and anterior temporal atrophy, in particular in the mesial and orbital prefrontal cortex, anterior insula and anterior cingulate cortices.³⁰

From a pathological point of view, bvFTD belongs to the group of frontotemporal lobe degenerations (FTLD), which are characterized by a circumscribed atrophy of

frontal and temporal cortex.²⁸ FTLN have two major histopathological subtypes: FTLN with tau-positive inclusions (FTLN-tau), and FTLN with ubiquitin-positive and TAR DNA-binding protein (TDP) inclusions, but Tau-negative inclusions (FTLN-TDP).²⁸ Alzheimer pathology is less frequently identified in patients clinically diagnosed as bvFTN.^{3,5,8,9} In agreement with these pathological data, it has been demonstrated that CSF biomarkers, which are considered surrogate markers of Alzheimer's pathophysiology, efficiently discriminate AD from bvFTN.³¹ In a previous study, we reported that only one out of 27 bvFTN patients presented a CSF AD biomarker profile.¹¹

These pathological observations of AD presenting with symptoms that mimic bvFTN have led to the concept of "frontal AD".^{8,25,26} Besides this behavioral variant, AD may also present as other non-amnesic atypical focal variants, such as posterior cortical atrophy and logopenic aphasia. Taken together, these observations emphasize that not all patients with AD manifest a "typical" clinical pattern and that patients sharing a common pathology may be clinically heterogeneous.⁶

Conversely, pathologically different neurological disorders may share common symptomatology. This is the case for typical AD and bvFTN. For instance, apathy, a common feature of bvFTN, is also frequently observed in AD, even at initial stages of the disease.³² On the other hand, recent evidence has shown that marked amnesia, a hallmark of AD, is not uncommon in bvFTN patients. Episodic memory performance has been traditionally considered relatively preserved in bvFTN and amnesia was considered an exclusion criterion for the clinical diagnosis of bvFTN.¹⁵ However, it is increasingly recognized that bvFTN patients exhibit amnesia,³³⁻³⁶ even at early stages of the disease as up to 10% of pathologically-proven cases of bvFTN reported memory deficits.³⁷ In a recent study, Hornberger, et al.³⁸ analyzed the structural integrity of the memory circuit in AD and FTLN *in vivo* and at *post-mortem*. Patients with FTLN and AD patients did not differ on memory measures (visual recall with the Rey-Osterrieth Complex Figure Test, visual recognition with the Doors and People Test, and immediate recall from the Rey Auditory Verbal Learning Test). Moreover, they found that FTLN and AD patients had similar degrees of hippocampal atrophy *in vivo*. More interestingly, they showed that FTLN had more severe hippocampal atrophy at *post-mortem*. In line with these observations, neuroimaging studies have previously demonstrated that measures of hippocampal volumes do not accurately distinguish AD and bvFTN patients.³⁹⁻⁴²

Taken together, for diagnostic purposes, the reliance on exclusively phenotypical features assessed by "topographical markers"⁷, such as episodic memory deficits and hippocampal atrophy, may lead to misdiagnosis between AD and bvFTN. Until the development of biomarkers, the *in vivo* diagnosis of neurodegenerative dementias had been largely based on the identification of the presenting cognitive profile supported by neuroimaging. However, the diagnosis established according only to clinical "phenotypical criteria", without reference to an accurate biomarker, may lack confidence, as not all patients with dementia syndromes manifest a "typical" clinical pattern. Moreover, patients sharing a common pathology may be clinically heterogeneous and, conversely, pathologically different diseases may share common symptoms. The correspondence between clinical phenotype and underlying pathology is not always optimal.⁵ Accordingly, new proposals for diagnostic criteria of AD^{7,43,44} include "pathophysiological markers" such as CSF biomarkers for increased diagnostic efficiency.

The CSF is the optimal source of biological physiopathological markers, as it is in direct contact with the cerebral extracellular space.⁴⁵ The neuropathological studies that analysed correlations of the levels of *in vivo* CSF biomarkers (total Tau [T-tau], phosphorylated Tau [P-Tau] and beta-amyloid peptide 1-42 [$A\beta_{42}$]) with the intensity of the *post-mortem* cerebral lesions showed that CSF biomarkers predicted the presence of AD pathologic features with high accuracy.⁴⁶⁻⁵⁰ Considering these data, CSF biomarkers can be considered surrogate markers of AD-associated pathologic changes in the brain.^{45,47-49}

The CSF levels of T-tau, P-Tau and $A\beta_{42}$ or, even more specifically, the combination of low $A\beta_{42}$ and high levels of T-tau and P-Tau, provide optimal sensitivity and specificity in the diagnosis of AD patients (even at MCI stage) against normal controls.^{51,52} The combined analysis of the CSF biomarkers, especially P-Tau/ $A\beta_{42}$ ratio, is also useful for the differential diagnosis between AD and frontotemporal lobar degeneration, regardless of its behavioural (bvFTN) or semantic presentation.^{11,31}

CSF biomarkers or amyloid imaging may also identify patients with Alzheimer underlying pathology in atypical focal cortical presentations of AD, and thus may identify eligible patients for emerging anti-amyloid therapies.^{10-12,23,53-57} Including pathophysiological markers in the clinical investigation of patients with suspected progressive cognitive and behavioural disorders seems crucial given the prospect of disease-modifying drugs that can target the physiopathological process of neurodegenerative diseases.^{58,59}

In this present series, all patients manifested typical bvFTD presentation and the diagnosis of atypical AD was possible only with CSF biomarker investigation. It is essential to use pathophysiological markers, especially in young subjects, in order to identify patients with atypical AD presentations and to propose a specific treatment for them.

While pathological data may be important for establishing diagnosis for patients, no autopsies were available in our cohort. It should be noted, however, that clinical diagnosis was established using accepted consensus criteria; all patients were extensively evaluated with clinical, biological, neuropsychological and

neuroimaging exams at a center with expertise in the field of dementias. Furthermore, we selected patients with strict biological inclusion criteria based on CSF biomarker results, such as reduced A β_{42} level, high P-Tau and abnormal P-Tau/A β_{42} ratio, which have been demonstrated to be highly correlated with Alzheimer pathology at *post-mortem* exam.⁴⁷

It would also be of value to compare the clinical and neuroimaging features across patients with frontal AD and bvFTD. Further studies with a greater number of patients are needed to investigate whether clinical, neuroimaging and neuropsychological parameters differ during disease progression of frontal AD and bvFTD.

REFERENCES

1. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med* 2010;362: 329-344.
2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
3. Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. *Brain*. 2007;130:2636-2645.
4. Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain* 2000;123:484-498.
5. Snowden JS, Thompson JC, Stopford CL, et al. The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. *Brain* 2011;134:2478-2492.
6. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011;10:785-796.
7. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010;9:1118-1127.
8. Grossman M, Libon DJ, Forman MS, et al. Distinct antemortem profiles in patients with pathologically defined frontotemporal dementia. *Arch Neurol* 2007;64:1601-1609.
9. Mendez MF, Joshi A, Tassniyom K, Teng E, Shapira JS. Clinicopathological differences among patients with behavioral variant frontotemporal dementia. *Neurology* 2013;80:561-568.
10. de Souza LC, Corlier F, Habert MO, Uspenskaya O, Maroy R, Lamari F, et al. Similar amyloid- β burden in posterior cortical atrophy and Alzheimer's disease. *Brain* 2011;134:2036-2043.
11. de Souza LC, Lamari F, Belliard S, et al. Cerebrospinal fluid biomarkers in the differential diagnosis of Alzheimer's disease from other cortical dementias. *J Neurol Neurosurg Psychiatry* 2011;82:240-246.
12. Rosenbloom MH, Alkalay A, Agarwal N, et al. Distinct clinical and metabolic deficits in PCA and AD are not related to amyloid distribution. *Neurology* 2011;76:1789-1796.
13. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51:1546-1554.
14. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;58:1803-1809.
15. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134:2456-2477.
16. de Souza LC, Volle E, Bertoux M, et al. Poor creativity in frontotemporal dementia: a window into the neural bases of the creative mind. *Neuropsychologia* 2010;48:3733-3742.
17. Bertoux M, Delavest M, de Souza LC, et al. Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry* 2012;83:411-416.
18. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology* 1988;38:900-903.
19. Reitan R. Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271-276.
20. Nelson HE. A modified card sorting test sensitive to frontal lobe defects. *Cortex* 1976;12:313-324.
21. Liberman J, Stewart W, Seines O, Gordon B. Rater agreement for the Rey-Osterrieth Complex Figure Test. *J Clin Psychol* 1994;50:615-624.
22. Peigneux P, Van der Linden M. Présentation d'une batterie neuropsychologique et cognitive pour l'évaluation de l'apraxie gestuelle. *Rev Neuropsychol* 2000;10:311-362.
23. Richard-Mornas A, Dirson S, Perret-Liaudet A, Decousus M, Thomas-Anterion C. Diagnosis contribution of biomarkers in Alzheimer disease: A case of frontotemporal dementia. *Rev Neurol (Paris)* 2011;167:160-163.
24. Raux G, Gantier R, Thomas-Anterion C, et al. Dementia with prominent frontotemporal features associated with L113P presenilin 1 mutation. *Neurology* 2000;55:1577-1578.
25. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol* 1999;56:1233-1239.
26. Taylor KI, Probst A, Miserez AR, Monsch AU, Tolnay M. Clinical course of neuropathologically confirmed frontal-variant Alzheimer's disease. *Nat Clin Pract Neurol* 2008;4:226-232.
27. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 2011;10:162-172.
28. Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. *J Neurol Neurosurg Psychiatry* 2011;82:476-486.
29. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain* 2005;128:1996-2005.
30. de Souza LC, Lehericy S, Dubois B, Stella F, Sarazin M. Neuroimaging in dementias. *Curr Opin Psychiatry* 2012;25:473-479.
31. Bian H, Van Swieten JC, Leight S, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* 2008;70:1827-1835.
32. Weiner MF, Hynan LS, Bret ME, White C 3rd. Early behavioral symptoms and course of Alzheimer's disease. *Acta Psychiatr Scand* 2005; 111:367-371.
33. Yew B, Alladi S, Shailaja M, Hodges JR, Hornberger M. Lost and Forgotten? Orientation versus Memory in Alzheimer's Disease and Frontotemporal Dementia. *J Alzheimers Dis* 2013;33:473-481.
34. Graham A, Davies R, Xuereb J, et al. Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* 2005;128:597-605.

35. Hornberger M, Piguet O. Episodic memory in frontotemporal dementia: a critical review. *Brain* 2012;135:678-692.
36. Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR. How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology* 2010;74:472-479.
37. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;56:399-406.
38. Hornberger M, Wong S, Tan R, et al. In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain* 2012;135:3015-3025.
39. Frisoni GB, Laakso MP, Beltramello A, Geroldi C, Bianchetti A, Soininen H, et al. Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology* 1999;52:91-100.
40. Laakso MP, Frisoni GB, Kononen M, et al. Hippocampus and entorhinal cortex in frontotemporal dementia and Alzheimer's disease: a morphometric MRI study. *Biol Psychiatry* 2000;47:1056-1063.
41. Lindberg O, Walterfang M, Looi JC, et al. Hippocampal shape analysis in Alzheimer's disease and frontotemporal lobar degeneration subtypes. *J Alzheimers Dis* 2012;30:355-365.
42. Davatzikos C, Resnick SM, Wu X, Parnip P, Clark CM. Individual patient diagnosis of AD and FTD via high-dimensional pattern classification of MRI. *Neuroimage* 2008;41:1220-1227.
43. Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270-279.
44. Jack CR, Jr., Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:257-262.
45. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat Rev Neurol* 2010;6:131-144.
46. Tapiola T, Overmyer M, Lehtovirta M, et al. The level of cerebrospinal fluid tau correlates with neurofibrillary tangles in Alzheimer's disease. *Neuroreport* 1997;8:3961-3963.
47. Tapiola T, Alafuzoff I, Herukka SK, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol* 2009;66:382-389.
48. Seppala TT, Nerg O, Koivisto AM, et al. CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. *Neurology* 2012;78:1568-1575.
49. Buerger K, Ewers M, Pirttila T, et al. CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. *Brain* 2006;129:3035-3041.
50. Strozzyk D, Blennow K, White LR, Launer LJ. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology* 2003;60:652-656.
51. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Mint-hon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol* 2006;5:228-234.
52. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* 2009;302:385-393.
53. Leyton CE, Villemagne VL, Savage S, et al. Subtypes of progressive aphasia: application of the international consensus criteria and validation using {beta}-amyloid imaging. *Brain* 2011;134:3030-3043.
54. Baumann TP, Duyar H, Sollberger M, et al. CSF-tau and CSF-Abeta(1-42) in posterior cortical atrophy. *Dement Geriatr Cogn Disord* 2010;29:530-533.
55. Rabinovici GD, Jagust WJ, Furst AJ, et al. A-beta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol* 2008;64:388-401.
56. Seguin J, Formaglio M, Perret-Liaudet A, et al. CSF biomarkers in posterior cortical atrophy. *Neurology* 2011;76:1782-1788.
57. Kas A, Uspenskaya O, Lamari F, et al. Distinct brain perfusion pattern associated with CSF biomarkers profile in progressive aphasia. *J Neurol Neurosurg Psychiatry* 2012;83:695-698.
58. Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTL. *Neurology* 2011;77:2034-2042.
59. Rowe CC, Ng S, Ackermann U, et al. Imaging beta-amyloid burden in aging and dementia. *Neurology* 2007;68:1718-1725.