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THESE POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE

Etude d'une cohorte française de patients présentant une dégénérescence lobaire fronto-temporale confirmée *post mortem*.

Analyse des corrélations clinico-pathologiques de leurs profils comportementaux.

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La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Sigles

AD	Alzheimer's disease
AGD	Argyrophilic grain disease
ALS	Amyotrophic latero-slcerosis
bv-FTD	Behavioral variant of frontotemporal degeneration
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CNIL	*Commission Nationale de l'Informatique et des Libertés*
CSF	Cerebrospinal Fluid
C9orf72	Chromosome 9 open reading frame 72
DLFT	Dégénérescence lobaire fronto-temporale
FTD	Frontotemporal degeneration
FTLD	Frontotemporal lobar degeneration
FUS	Fused-in-Sarcoma
LBD	Lewy body dementia
MAPT	Microtubule-associated protein tau
MMRC	Memory resource and research center
nf-FTD	Non fluent variant of Frontotemporal degeneration
OR	Odds ratio
PGRN	Progranulin
PSP	Progressive supranuclear palsy
PSPS	Progressive supranuclear palsy syndrome
SD	Standard deviation
sv-FTD	Semantic variant of frontotemporal degeneration
Tau	Tubulin Associated Unit

TDP-43 TAR DNA-binding protein 43

Sommaire

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Titre de la Thèse : Etude d'une cohorte française de patients présentant une dégénérescence lobaire fronto-temporale confirmée *post mortem*. Analyse des corrélations clinico-pathologiques de leurs profils comportementaux.
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Résumé :

Contexte : Les dégénérescences lobaires fronto-temporales (DLFT) constituent un groupe hétérogène de maladies neurodégénératives. La prédiction de la nature des lésions neuro-pathologiques sous-jacentes reste difficile du vivant des patients. Cette étude a pour objectif de décrire une population française de patients présentant une DLFT confirmée *post mortem* et d'étudier la corrélation entre le diagnostic neuro-pathologique et le profil comportemental, apathique et/ou désinhibé des patients.

Matériel et Méthodes : Nous avons recensé les patients présentant une DLFT confirmée post mortem entre 1993 et 2021 auprès de 5 Centres de mémoire de ressources et de recherche (CMRR) en France. Nous avons collecté rétrospectivement leurs données cliniques, neuro-pathologiques et génétiques. Nous avons ensuite réalisé une comparaison par sous-groupes neuro-pathologiques (TDP A/B, TDP C, PSP/DCB, Pick, AGD) concernant les données démographiques, les présentations cliniques initiales, les profils comportementaux et les critères cliniques de Rascovsky.
Résultats : 114 patients ont été inclus, il y avait 35% de femmes, l'âge moyen de début était de 60 ans et la durée moyenne d'évolution de la maladie était de 10 ans, 17% avait une mutation génétique. Il y avait 49% de DLFT-TDP, 46% de DLFT-Tau et 5% de DLFT-FUS. Nous avons comparé les 5 sous-groupes neuro-pathologiques, il y avait une différence significative concernant l'âge de début des symptômes ($p<0,0001$), la durée d'évolution de la maladie ($p=0,0029$), la présentation comportementale ($p=0,0169$) et mnésique ($p=0,0051$) initiale et les profils comportementaux ($p=0,0072$).
Conclusion : Les caractéristiques de notre population correspondent aux données de la littérature. Notre étude confirme la mauvaise corrélation entre les diagnostics cliniques initiaux et neuro-pathologiques. L'analyse statistique que nous avons menée comparant les sous-groupes neuro-pathologiques en fonction des profils comportementaux, des présentations cliniques initiales et des données démographiques a montré que les DLFT-TDP type C et les maladies de Pick avaient majoritairement un profil désinhibé, les AGD et PSP/DCB avaient majoritairement un profil apathique, les AGD avaient principalement une présentation amnésique initiale. De prochaines études associant les données de bilans neuropsychologiques, orthophoniques et de neuroimagerie pourraient permettre d'affiner les résultats, en attendant le développement de nouveaux biomarqueurs et de nouvelles techniques de neuroimagerie.

Composition du Jury :

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Introduction

Les dégénérescences lobaires fronto-temporales (DLFT) correspondent à un groupe hétérogène de pathologies qui sont caractérisées par la dégénérescence préférentielle des régions frontales et temporales antérieures. Ces pathologies diffèrent les unes des autres par leurs présentations cliniques ainsi que les anomalies génétiques et anatomopathologiques en cause. Les DLFT sont la 3è cause de démence du sujet jeune (avant 65 ans) après la maladie d'Alzheimer et la démence vasculaire [1]. La prévalence est estimée à 15-22/100 000 [2]. La durée d'évolution de la maladie varie de 2 à 20 ans avec une durée moyenne de 8 ans [3]. Au cours des dernières années, le cadre nosologique des DLFT n'a cessé de progresser compte tenu de découvertes majeures dans le domaine de la génétique et de la neuro-pathologie. De même, la description clinique et les profils neuropsychologiques des patients atteint de DLFT se sont largement affinés.

Il existe 3 phénotypes cliniques principaux, le variant comportemental et deux variants langagiers, qui correspondent au variant non fluent d'aphasie primaire progressive et au variant sémantique d'aphasie primaire progressive [4].

Le diagnostic « probable » de DLFT comportementale est défini, selon les critères de Rascovsky *et al* de 2011, par l'association de troubles du comportement et des interactions sociales précoces, un syndrome dysexécutif et des examens de neuro-imagerie caractéristiques [5]. Les troubles du comportement et des interactions sociales sont définis selon 5 critères : la désinhibition, l'apathie, la perte d'empathie, les stéréotypies verbales ou motrices et les modifications du comportement alimentaire [5].

Le variant non-fluent d'aphasie primaire progressive est défini par un discours laborieux, un agrammatisme ou une apraxie de la parole. Le variant sémantique ou démence sémantique est défini par un trouble de la compréhension des mots et un trouble de la dénomination [6].

Enfin, les DLFT comportent également des présentations motrices telles que la paralysie supranucléaire progressive, le syndrome corticobasal et la sclérose latérale amyotrophique [4].

Il existe une histoire familiale dans 30 à 50% des cas mais une mutation génétique n'est retrouvée que dans 10 à 20% des cas [7]. Les mutations ont été identifiés dans 3 principaux gènes : *microtubule-associated protein tau* (MAPT), *progranulin* (GRN) et *chromosome 9 open reading frame 72* (C9orf72) [8].

Le processus neuro-pathologique mis en cause dans les DLFT correspond à l'accumulation intracellulaire anormale de protéines induisant une mort neuronale. La classification anatomopathologique actuelle des DLFT comptabilise 3 groupes caractérisés par le type de protéine en cause : *Tubulin Associated Unit* (Tau), *TAR-DNA-binding protein 43* (TDP-43) et *fused-in-sarcoma* (FUS) [9].

Les DLFT-TDP représentent la majeure partie des DLFT (plus de 50% des cas) et sont subdivisées en quatre groupes, en fonction de la localisation et de la morphologie des inclusions (Type A, B, C ou D).

Les DLFT-Tau représentent environ 40% des cas et sont divisées en deux groupes, selon la présence de trois ou quatre domaines de répétition (3R ou 4R) [9,10]. Les patients ayant une mutation MAPT présentent une accumulation de Tau caractéristique et peuvent donc être classé à part sur le plan neuro-pathologique.

Depuis plusieurs années, de nombreuses études ont été menées afin d'améliorer les corrélations anatomocliniques dans l'espoir de mieux prédire le diagnostic neuro-pathologique du vivant des patients. Outre l'amélioration des connaissances concernant l'évolution et le pronostic de chaque sous type histologique, prédire la pathologie sous-jacente pourrait un jour permettre d'envisager des traitements curatifs. En effet, l'avènement des immunothérapies ciblées laisse espérer des thérapeutiques prometteuses pour atteindre spécifiqueemnt les protéines pathologiques en cause dans les DLFT et empêcher leur évolution [11].

Cependant, à ce jour, ni la clinique, ni les biomarqueurs spécifiques du liquide céphalorachidien (LCR), ni l'imagerie ne permettent de distinguer avec assez de certitude les différents sous-types neuro-pathologiques [12–14].

Nous croyons qu'il est possible encore d'affiner les descriptions sémiologiques des patients afin de mieux prédire la pathologie sous-jacente.

Nous avons notamment constaté que 2 des 5 critères cliniques des critères de Rascovsky que sont l'apathie et la désinhibition sont décrit dans l'ensemble des présentation cliniques de DLFT [5,6,15,16]. Ils aboutissent à des tableaux cliniques contrastés. Des études cliniques et radiologiques se sont attardés sur ces signes sémiologiques mais il n'existe pas de données quant à leur corrélation avec un sous-type neuro-pathologique [17–21].

C'est pourquoi nous présentons une étude multicentrique de patients présentant une DLFT confirmée post-mortem avec pour objectif : *(i)* de décrire la population concernant les données démographiques, les antécédents personnels et familiaux, la génétique et le diagnostic clinique initial, et *(ii)* étudier la corrélation entre le diagnostic neuro-pathologique et le profil comportemental, apathique et/ou désinhibé des patients.

Article en Anglais

1 Introduction

Frontotemporal degeneration (FTD) is the third early-onset dementia (first symptoms before 65) after Alzheimer's disease and vascular dementia [1]. It is a neurodegenerative disease that leads to a frontal and temporal atrophy [22]. FTD refers to a heterogenous group of disease that includes a behavioural variant (bv-FTD) and two language subtypes: the semantic variant (sv-FTD) and the non-fluent variant (nf-FTD) [5,6,23]. FTD patients can also present motor disorders including progressive supranuclear palsy syndrome (PSPS), cortico-basal syndrome (CBS) or amyotrophic lateral sclerosis (ALS) (associated with bv-FTD) [4,15,16,23].

In the last decades, the understanding of the underlying pathophysiology of this group of diseases improved greatly [9,10]. The main pathogenic process suggested is the accumulation of intracellular protein inclusions which leads to neuronal death. Three proteins have been identified: Tubulin Associated Unit (Tau), TAR-DNA-binding protein 43 (TDP-43) and fused-in-sarcoma (FUS) [24]. Frontotemporal Lobar Degeneration due to an accumulation of Tau (FTLD-Tau) are divided into 2 subtypes, depending on the isoforms within the inclusions: Tau 3R represented by Pick's disease and Tau 4R which includes progressive supranuclear palsy PSP, cortico-basal degeneration (CBD) and argyrophilic grain disease (AGD). Patients with microtubular associated-tubule (MAPT) gene mutations present accumulation of Tau, Tau 3R, Tau 4r or both, they are described as a specific category of FTLD-Tau. Frontotemporal Lobar Degeneration due to the accumulation of TDP (FTLD-TDP) are divided into 5 subtypes depending on the shape and the location of the inclusions: A, B, C, D or undetermined [25].

Nowadays, the challenge focuses on the improvement of the clinicopathological correlations. Being able to predict the cause of an FTD presentation at the molecular level would allow the physician to consider specific treatment targeting the pathogenic protein. Despite the research that has been conducted in the last years, neither specific cerebrospinal fluid (CSF) biomarkers, nor cerebral imaging allow the clinician to predict the underlying pathology [12–14]. Only detection of specific genetic mutations such as (Chromosome 9 open reading frame 72 (C9orf72), progranulin (PGRN) and Microtubule-associated protein tau (MAPT) enable physicians to confirm diagnosis. However genetic mutations concern a minority of FTD patients as it is 10-20% of all patients with FTD [7].

We believe that investigations on clinical symptoms can be improved especially regarding behavioural symptoms in order to provide a better prediction of the underlying pathology.

Previous studies showed that some clinical presentations appear to be more specific of one subtype of protein inclusion. A PSP syndrome (PSPS) has a high correlation with PSP. However extrapyramidal features are equally common in FTLD-TDP and FTLD-Tau [26]. Semantic dementia associated to loss of sympathy/empathy, compulsive behaviour and asymmetric anterior temporal atrophy is correlated to FTLD-TDP type C [26,27]. ALS associated to bv-FTD is described only in patients with FTLD-TDP [28,29]. Patients with FTLD-FUS tend to start symptoms younger and have more severe behavioural impairment [29,30]. Perry *et al* showed in 2017, that a bv-FTD presentation can be associated to any FTLD subgroup, but also to Alzheimer's disease for example [26].

The behavioural variant (bv-FTD) is the most frequent variant of all FTD subtypes [4]. It is defined by the presence of behavioural symptoms, a dysexecutive profile and a

frontal atrophy/hypometabolism on imaging [5]. In the early descriptions of bv-FTD, two contrasting behavioural disturbances have been described: apathetic and disinhibited manifestations [21,22,31]. Apathy can be defined as diminished motivation, interest, action initiation and emotional reactivity [32]. Disinhibition includes socially inappropriate behaviour, loss of manners, or impulsive, rash or careless actions [5].

The neuroanatomical correlates of apathy and disinhibition vary among studies, depending on whether they focused on grey matter, white matter or a combination of both [17–19]. Zamboni *et al* suggested that apathy is associated with atrophy in dorsolateral prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex which causes difficulty to elaborate and execute goal directed behaviours [20]. In contrast, disinhibition is correlated with atrophy in the right mediotemporal structures (amygdala and hippocampus) and the right nucleus accumbens (ventral striatum) which causes impaired risk perception and reward/punishment attribution mechanisms and may occur independently from prefrontal dysfunction [20].

These two symptoms are common in every FTD variant and they provide two contrasting patients profiles that can be easily identified by the clinician [6,15,16,26]. If we show a correlation between an apathetic or disinhibited profile with the underlying pathology, we believe that it could help physicians to classify patients between FTLD-Tau and FTLD-TDP.

To our knowledge, specific correlations between an apathetic or a disinhibited profile and underlying pathology has not been studied yet. Moreover, prior studies on clinicopathological correlations preceded updated neuropathological criteria or only involved a small sample number of patients [26,28,33–39]. The latest study from Perry *et al* in 2017 analysed patients with a clinical bv-FTD diagnosis, 117 of them had

autopsy data and pathological diagnostic of FTLD was confirmed for 98 (15 had Alzheimer's disease) [26].

We established a French multicentric study of a large number of patients with confirmed neuropathological FTLD diagnosis. The goals of this study were: (*i)* to describe this population according to demographic features, personal and family medical history, genetic and initial clinical diagnosis and (*ii)* to assess correlation between neuropathological diagnosis and behavioural profile regarding apathy and/or disinhibition.

2 Material and methods

2.1 Study design

We have conducted a multicentric observational retrospective study. We included patients with neuropathological evidence of FTLD at autopsy between January 1, 1993 and July 31, 2021 from 5 French Memory Resource and Research Center (MRRC) in Lille-Bailleul, Marseille, Colmar, Paris (La Pitié Salpétrière hospital) and Angers. Exclusion criteria included the lack of final neuropathological analysis, lack of substantial follow up with clinical data in the medical record as well as the impossibility to categorize patient in any of the four behavioural subgroups described below.

Post mortem cerebral examinations were performed in the five different MRRC and neuropathological analysis were based on international classifications [9,10]. Patients were classified according to immunoreactive inclusions into two major groups FTLD-Tau, FTLD-TDP. Patients with an autopsy performed before 2006 underwent a new analysis in order to see if any TDP-43 or FUS inclusions can be observed, since these immunoreactive inclusions were first described in 2006. We then harmonized the

results for the FTLD-TDP classification based on the latest Mackenzie classification [25].

2.2 Retrospective analysis of clinical records

Medical records were examined by two neurology residents (GF, BH) from the MRRC of Lille. Demographics features including sex, age of onset, education, disease duration (calculated between age at onset and age at death), family history of cognitive impairment and psychiatric disorder, as well as cardiovascular risk factors and neurological and psychiatric medical history were collected.

Cognitive and behavioural symptoms reported in the records were categorized according to Rascovsky's criteria and their subcategories [5]:

- Early behavioural disinhibition, including: socially inappropriate behaviour, loss of manners or decorum, impulsive, rash or careless actions, reckless spending, sexual disinhibition
- Early apathy or inertia,
- Early loss of empathy or sympathy
- Early perseverative, stereotyped or compulsive/ritualistic behaviour including: simple repetitive movements, complex, compulsive or ritualistic behaviours, stereotypy of speech
- Hyperorality and dietary changes such as altered food preferences, binge eating, increased consumption of alcohol or cigarettes, oral exploration or consumption of inedible objects.

Additionally, mentions of a subjective memory complaint and a prominent semantic impairment or any other speech impairment were collected. We also collected

psychiatric symptoms and relevant signs reported upon neurological examination such as apraxia, pyramidal signs, parkinsonism.

With these data, we established the initial clinical presentation. It was assigned to each patient depending on the first and prominent symptom and/or the first clinical diagnosis mentioned in medical record. In case of discrepancy between first symptom and first clinical diagnosis, a presentation was assigned after rereading medical record. There appeared to be five different presentations, defined as:

- Behavioural presentation: patients with first symptom, behavioural or psychiatric impairment and/or first diagnosis mentioning psychiatric disorder or bv-FTD.
- Non-semantic aphasia: patients with first symptom, dysarthria or anarthria (when both symptoms were prominent compared to motor symptoms), or aphasia and first diagnosis nf-FTD, CBS, PSPS.
- Semantic aphasia: patients with first symptom, semantic aphasia and/or first diagnosis semantic dementia
- Motor presentation: patients with first symptom, fall, walking disorder, parkinsonian syndrome, dysarthria, anarthria (when not prominent) and first diagnosis of CBS or PSPS.
- Amnesic presentation: patients with first symptom memory impairment and/or first diagnosis of AD.

Diagnosis of ALS was analysed separately from these initial clinical presentations.

Every medical history was discussed with each patient's neurologist in order to ensure that encoding was consistent with the physician understanding of the patient.

2.3 Behavioural categorization

Patients were categorized into four groups of behavioural profile: apathetic, disinhibited, apathetic and disinhibited or none. Classification was based on the most prominent symptom at onset and during the first 3 years of the disease according to medical records and to the referring neurologist.

2.4 Data Analysis

We performed a descriptive analysis of the four behavioural profiles based on the clinical data collected. Then we analysed the correlation between these four groups, 11 other variables (sex, age of onset, disease duration, early loss of empathy or sympathy, early perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality or dietary change, and initial presentation such as: semantic presentation, non-semantic presentation, motor presentation, amnesic presentation) and the neuropathological diagnosis (FTD-Tau and FTD-TDP). In the bivariate and multivariate analyses, FTLD-FUS, MAPT and FTLD-TDP U were excluded because of an insufficient sample size.

2.5 Statistical analysis

2.5.1 Univariate analyses

We first determined the baseline characteristics. Qualitative, binary, or discrete variables are expressed in numbers and percentages. Quantitative variables are expressed as mean and standard deviation (SD) if the histogram reveals a symmetrical pattern distribution, otherwise the median with the first and third quartile (Q1, Q3) were used.

2.5.2 Bivariate analyses

FTLD-Tau patients have been compared with patients with FTLD-TDP patients. FTLD-TDP and FTLD-Tau subtypes were also compared, they were classified as FTLD-TDP type A/B, FTLD-TDP type C, PSP/CBD, Pick's disease and AGD. Independence between two qualitative variables was tested using a Chi-square or an exact Fisher test (in case of a theoretical sample size <5). Independence between two quantitative variables was tested using a Student test or a Wilcoxon-Mann-Whitney test (in case of a non Gaussian distribution). Quantitative variables were compared by a variance analysis or a Kruskal-Wallis test (in case of a non Gaussian distribution), qualitative variables by Chi-square or an exact Fisher test.

2.5.3 Multivariate analyses

Relationships between candidate covariates and a binary variable are modelled and tested using logistic regression. The results are expressed in terms of odds ratios (OR) with 95% confidence intervals. Only the covariates associated with the variable of interest, in the bivariate analysis, with a *p* value lower than 20% are included in the analysis.

2.5.4 Significance

Statistical tests are bilateral. The *p* values are considered significant at the 5% threshold. Confidence intervals are calculated at 95%.

Data were analyzed with SAS software version 9.4.

2.6 Regulatory framework

This study complies with MR004, edited by the Commission Nationale Informatique et Libertés (CNIL). The patient did not express an opposition to the re-use of their clinical data for research purpose during their lifetime. The MRRC of Lille centralized all data and data sharing agreements *ex gratia* with the 4 other MRRCs were set up Our study was declared on the Health Data Hub platform (https://www.health-data-hub.fr/projets/correlations-anatomo-cliniques-dans-le-spectre-des-degenerescences-lobaires-fronto). Data will be stored for 2 years after publication and then archived with limited access.

3 Results

3.1 Characteristics of patients at inclusion

Figure 1. Flowchart

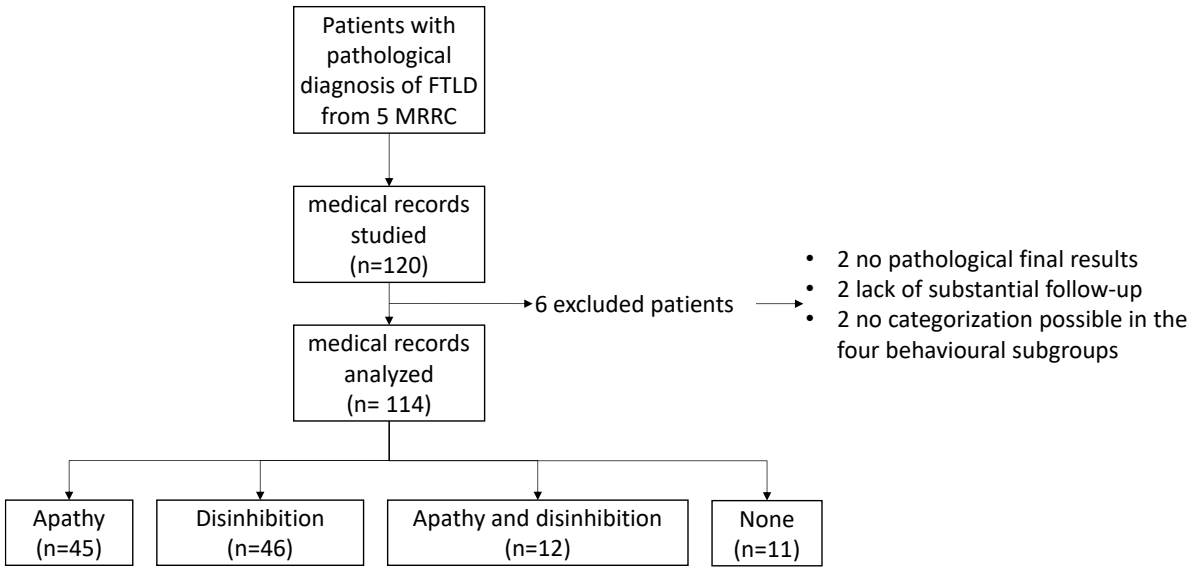


Table 1. Baseline characteristics in the overall population

	All (n= 114)
Demographic features	
Women, n (%)	44 (39)
Education, n (%)	
< Certificat d'étude	49 (43)
Bac-Bac + 2	25 (22)
> Bac +2	28 (25)
Medical History	
Hypertension, n (%)	28 (25)
Smoke, n (%)	25 (22)
Alcohol and/or drug, n (%)	11 (10)
Type 2 diabetes, n (%)	11 (10)
Dyslipidemia, n (%)	22 (19)
Psychiatric disorder, n (%)	25 (22)
Family cognitive impairement, n (%)	47 (41)
Family psychiatric disorder, n (%)	18 (16)
Clinical characteristics	
Age at first symptom, m (sd)	59 (10.1)
Disease duration, m (sd)	10 (5.9)
Initial clinical presentation, n (%)	
Behavioral	57 (50)
Non semantic aphasia	19 (17)
Amnesic	16 (14)
Motor	14 (12)
Semantic aphasia	8 (7)
ALS diagnosis, n (%)	13 (11)
Gene mutation	18 (16)
MAPT	1 (1)
PGRN	7 (6)
C9orf72	10 (9)
Histopathological diagnosis	
Tau, n (%)	52 (46)
CBD	14 (12)
PSP	13 (11)
AGD	11 (10)
Pick's disease	11 (10)
MAPT	2 (2)
Undetermined	1 (1)
TDP, n (%)	56 (49)
type A	25 (22)
Type B	17 (15)
Type C	11 (10)
Undetermined	3 (3)
FUS, n (%)	6 (5)

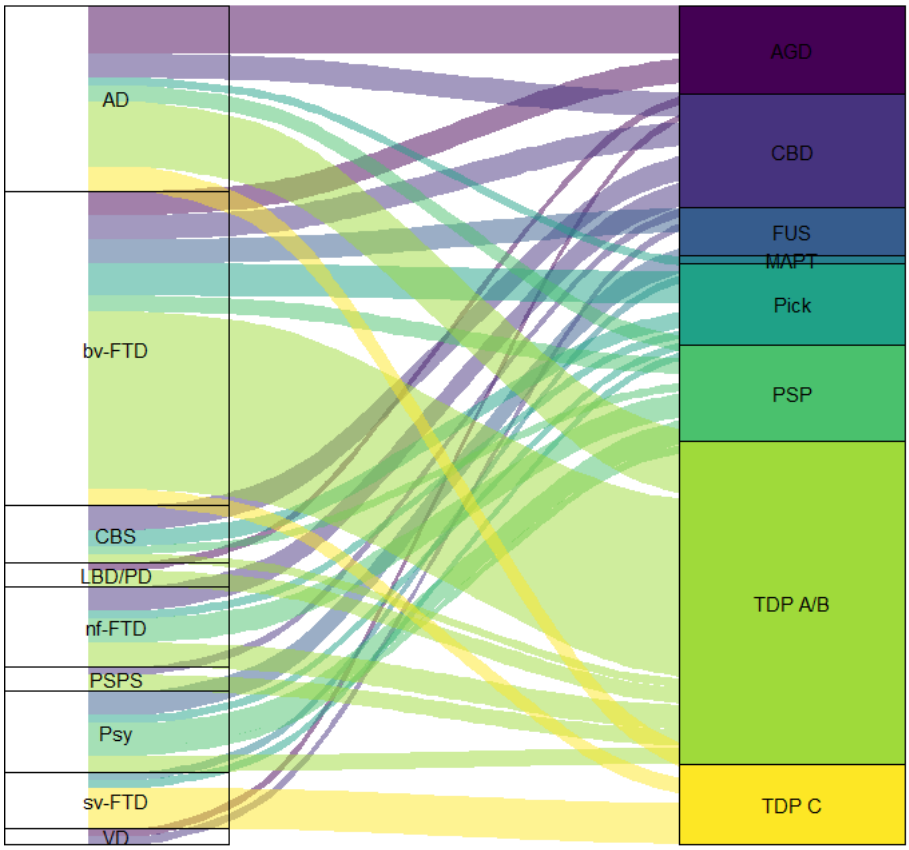
n : number, m : mean, sd : standard deviation, ALS : amyotrophic latero-sclerosis, Tau : tubulin associated unit, CBD: corticobasal degeneration, PSP : progressive supranuclear palsy, AGD : argyrophilic grain disease, MAPT : microtubule-associated protein tau , TDP : TAR DNA-binding protein FUS : Fused-in-sarcoma

As shown on table 1, in the overall patient population, there were 39% of women, the mean age at first symptom was 59 years, mean disease duration was 10 years. Sixteen percent of all patients had a genetic mutation correlated to FTD (9% of C9orf72, 6% of PGRN, 1% of MAPT mutations). Twenty-two percent had a history of psychiatric disorder and 41% had a family cognitive impairment. Eleven percent had a diagnosis of Amyotrophic latero-sclerosis (ALS). Regarding the initial clinical presentation there were 50% of behavioural presentation, 17% of non-semantic aphasia, 14% of amnesic presentation, 12% of motor presentation, 7% of semantic aphasia.

Fifty-two (46%) patients had FTLD-Tau diagnosis: 14 CBD, 13 PSP, 11 AGD, 11 Pick's disease, 2 MAPT and 1 undetermined. There were 56 (49%) FTLD-TDP of which 42 (37%) type A/B (25 type A, 17 type B), 11 (10%) type C and 3 (3%) undetermined. There were 6 (5%) FTLD-FUS.

There were 11 initial different diagnoses (Annexe 1) of which 43 were bv-FTD, 23 Alzheimer's disease, 10 nf-FTD, 9 semantic dementia, 7 CBS, 6 PSPS, 5 psychiatric disorders (other than depressive disorder), 3 vascular dementia, 2 depressive disorder, 2 Lewy Body dementia (LBD), 1 Parkinson's disease.

Figure 2. Distribution of the neuropathological diagnosis among the initial clinical diagnosis



AD : Alzheimer's disease, CBS : corticobasal syndrome, LBD : Lewy Body dementia, MP : Parkinson's disease, nf-APP : non-fluent primary progressive aphasia, PSPS : progressive supranuclear palsy syndrome, psy : psychiatric disorder, sv-FTD : semantic variant of frontotemporal dementia, VD : vascular dementia, Tau : tubulin associated unit, CBD: corticobasal degeneration, PSP : progressive supranuclear palsy, AGD : argyrophilic grain disease, MAPT : microtubule-associated protein tau , TDP : TAR DNA-binding protein, FUS : Fused-in-sarcoma

As shown on Figure 2 and annexe 1 initial diagnoses were not correlated to neuropathological diagnosis.

Regarding patients with diagnosis of bv-FTD (n=43), 27 (64%) were diagnosed with FTLD-TDP (22 (52%) type A or B, 2 (5%) type C, 3 (7%) type U), 12 (29%) as FTLD-Tau of which 4 (10%) were Pick's disease and 8 (19%) were Tau 4R. Five (56%) patients with initial diagnosis of sv-FTD were diagnosed with FTLD-TDP type C, but 2 (22%) were FTLD-Tau (1 MAPT, 1 Pick's disease). We noticed that 7 (70%) patients

with initial diagnosis of nf-FTD were FTLD-Tau (6 Tau 4R, 1 Pick's disease), however 3 (30%) were FTLD-TDP type A/B on the neuropathological analysis.

Regarding motor presentations, a majority of patients (6, 86%) with initial diagnosis of CBS were diagnosed as FTLD-Tau (4 Tau 4R, 2 Pick's disease), the remaining one was a FTLD-TDP type A; 4 (67%) patients with initial diagnosis of PSPS were diagnosed with Tau 4R, 2 (33%) as FTLD-TDP type A/B. Fifty-six percent of patients with initial diagnosis of Alzheimer's disease were FTLD-Tau, 43% were FTLD-TDP.

Concerning patients diagnosed with a psychiatric disorder a majority of them were FTLD-FUS (3, 60%).

3.2 Characteristics of patients in each behavioural profile group

Table 2. Baseline characteristics of the different behavioural profile groups

Behavioral Profile	Apathy (n=45)	Disinhibition (n=46)	Apathy and disinhibition (n=12)	None (n=11)
Demographic features				
Women, n (%)	12 (27)	22 (48)	4 (33)	6 (55)
Medical History				
Psychiatric disorder, n (%)	10 (22)	7 (15)	5 (42)	3 (27)
Family cognitive impairement, n (%)	18 (40)	23 (50)	4 (33)	2 (18)
Family psychiatric disorder, n (%)	4 (9)	12 (26)	1 (8)	1 (9)
Clinical characteristics				
Age at first symptom, m (sd)	61 (9.7)	56 (9.2)	57 (10.8)	65 (10.4)
Disease duration, m (sd)	10 (5.5)	11 (7)	8 (4.3)	8 (2.6)
ALS diagnosis, n (%)	4 (9)	6 (13)	3 (25)	0
Initial clinical presentation, n (%)				
Behavioral	17 (38)	30 (65)	11 (92)	0 (0)
Non semantic aphasia	9 (20)	7 (15)	1 (8)	2 (18)
Amnesic	10 (22)	6 (13)	0 (0)	0 (0)
Motor	5 (16)	0 (0)	0 (0)	6 (55)
Semantic aphasia	2 (4)	3 (7)	0 (0)	3 (27)
Psychiatric symptoms, n (%)				
Depression	8 (18)	7 (15)	0	2 (18)
Euphoria	0	4 (9)	1 (8)	0
Agression	5 (11)	11 (24)	4 (33)	2 (18)
Mood lability	0	3 (7)	0	0
Anxiety	13 (29)	6 (13)	1 (8)	2 (18)
Irritability	14 (31)	17 (37)	0	1 (9)
Gene mutation				
MAPT, n (%)	0 (0)	1 (2)	0 (0)	0 (0)
PGRN, n (%)	6 (13)	1 (2)	0 (0)	0 (0)
C9orf72, n (%)	6 (13)	3 (7)	1 (8)	0 (0)
Histopathological diagnosis				
Tau, n (%)	25 (56)	14 (30)	5 (42)	8 (73)
4R	21 (48)	8 (17)	4 (33)	5 (46)
Pick's disease	2 (5)	5 (11)	1 (8)	3 (27)
MAPT	1 (3)	1 (2)	0	0
TDP, n (%)	20 (44)	28 (61)	5 (42)	3 (27)
Type A/B	18 (41)	20 (44)	3 (25)	1 (9)
Type C	2 (5)	6 (13)	1 (8)	2 (18)
Type U	0	2 (4)	1 (8)	0
FUS, n (%)	0	4 (9)	2 (17)	0

n : number, m : mean, sd : standard deviation, ALS : amyotrophic latero-sclerosis, Tau : tubulin associated unit, 4R : FTLD-Tau 4R (four repetitions), MAPT : microtubule-associated protein tau , TDP : TAR DNA-binding protein FUS : Fused-in-sarcoma, type U : undetermined type

As shown on table 2, 45 (39%) patients had an apathetic profile, 46 (40%) a disinhibited profile, 12 (11%) an association of both and 11 (9%) none.

Patients with a disinhibited profile (with or without apathy) were mostly described with a behavioural initial presentation, 30 (65%) and 11 (92%) respectively. Disinhibited patients were not described with motor initial presentation, whereas motor presentation

was predominant in patients without apathy or disinhibition (55%). No behavioural presentation was described in patients without apathy or disinhibition.

Apathetic profile was found in every initial clinical presentation with a majority of behavioural presentation (17, 38%) and a minority of semantic aphasia (2, 4%). Amnestic presentations were described in patients with an apathetic profile (10, 22%) or a disinhibited profile (6, 13%).

Regarding psychiatric profile, depression was as frequent in apathetic profile (8, 18%) as in disinhibited group (7, 15%). Anxiety was described in every profile, it was more frequent in apathetic profile (13, 29%) than in disinhibited profile (6, 13%). Euphoria was described only in disinhibited profile (4, 9%) and disinhibited and apathetic profile (1, 8%). Irritability was described in disinhibited profile (17, 37%) as in the apathetic profile (14, 31%). Aggression was described in every profile.

3.3 Clinicopathological correlation

3.3.1 Characteristics of all neuropathological subgroups

Table 3. Baseline characteristics of neuropathological diagnosis

	TDP A/B N=42	TDP C N=11	TDP U N=3	Tau 4R N=38	Pick N=11	MAPT N=2	FUS N=6
Demographic features							
Women, n (%)	15 (36)	3 (27)	2 (67)	16 (42)	4 (36)	0	4 (67)
Medical History							
Psychiatric disorder, n (%)	8 (19)	1 (9)	1 (33)	8 (21)	2 (18)	1 (50)	3 (50)
Family cognitive impairement, n (%)	23 (55)	4 (36)	3 (100)	12 (32)	3 (27)	1 (50)	1 (17)
Family psychiatric disorder, n (%)	8 (19)	1 (9)	0	8 (21)	1 (9)	0	0
Clinical characteristics							
Age at first symptom, m (sd)	57 (7.9)	61 (6.6)	56 (11.2)	65 (9.2)	55 (7.1)	51 (1.4)	41 (10.1)
Disease duration, m (sd)	9 (6.8)	12 (3.1)	5 (1.15)	11 (5.8)	12 (4.8)	17 (3.5)	6 (2.2)
ALS diagnosis, n (%)	12 (29)	0	1 (33)	0	0	0	0
Initial clinical presentation, n (%)							
Behavioral	27 (64)	4 (36)	3 (100)	10 (26)	7 (64)	0	6 (100)
Non semantic aphasia	5 (12)	2 (18)	0	11 (26)	2 (18)	0	0
Amnesic	5 (12)	0	0	12 (26)	0	1 (50)	0
Motor	4 (10)	0	0	8 (21)	1 (9)	0	0
Semantic aphasia	1 (2)	5 (46)	0	0	1 (9)	1 (50)	0
Behavioral profile, n (%)							
Apathy	18 (43)	2 (18)	0	21 (55)	2 (18)	1 (50)	0
Disinhibition	20 (48)	6 (55)	2 (67)	8 (21)	5 (46)	1 (50)	4 (67)
Apathy and disinhibition	3 (7)	1 (9)	1 (33)	4 (11)	1 (9)	0	2 (33)
None	1 (3)	2 (18)	0	5 (13)	3 (27)	0	0
Loss of empathy, n (%)	24 (57)	5 (46)	1 (33)	17 (45)	7 (64)	2 (100)	5 (83)
Perseverative behaviour, n (%)	24 (57)	7 (64)	2 (67)	21 (55)	8 (73)	2 (100)	4 (67)
Dietary changes, n (%)	27 (64)	8 (73)	2 (67)	20 (53)	6 (55)	2 (100)	6 (100)
Gene mutation							
MAPT, n (%)	0	0	0	0	0	1 (50)	0
PGRN, n (%)	7 (17)	0	0	0	0	0	0
C9orf72, n (%)	8 (19)	0	2 (67)	0	0	0	0

n : number, m : mean, sd : standard deviation, ALS : amyotrophic latero-sclerosis, TDP : TAR DNA-binding protein, TDP A/B : FTLD TDP type A or B, TDP C : FTLD TDP type C, TDP U : FTLD-TDP undetermined, Tau : tubulin associated unit, TAU 4R : FTLD-Tau 4R, MAPT : microtubule-associated protein tau , FUS : Fused-in-sarcoma

As shown in table 3, FTLD-FUS patients had the youngest age of onset (41 years) whereas FTLD-Tau 4R were the oldest (65 years). FTLD-FUS patients had the shortest mean's disease duration (6 years) and MAPT patients had the longest (17 years).

Forty-two (64%) FTLD-TDP type A/B patients were described with behavioural initial presentation. Every other initial presentation was also described in this subgroup of patients. Five (46%) patients with FTLD-TDP type C were initially described with

semantic aphasia, 4 (36%) were described with behavioural presentation and 2 (18%) with non-semantic aphasia. FTLD-Tau 4R (n=38) could be any presentation except semantic aphasia. Seven (64%) patients with Pick's disease were described with behavioural initial presentation, every other initial presentation was described except amnesic presentation. Only two patients with MAPT were described, one (50%) with semantic aphasia and the other (50%) with amnesic presentation. Regarding FTLD-FUS, 6 (100%) patients had a behavioural presentation.

Four (67%) FTLD-FUS were described with disinhibited profile and 2 (33%) with apathetic and disinhibited profile. Loss of empathy was described in 5(83%) of FTLD-FUS and 2 (100%) MAPT. Early perseverative, stereotyped or compulsive behaviour was described in 2 (100%) and 4 (67%) FTLD-FUS. Hyperorality and dietary changes were described in 2 and 6 (100%) patients with MAPT and FTLD-FUS.

3.3.2 Bivariate analysis for clinicopathological correlation with behavioural profile and the other Rascovsky's criteria

Bivariate analysis was performed to compare neuropathological subgroups depending on their behavioural profiles, sex, age of onset, disease duration, early loss of empathy or sympathy, early perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality or dietary change, and the initial clinical presentation. FTLD-FUS and MAPT were excluded of this analysis because they were there sample of patients were too small.

We first analysed FTLD-Tau versus FTLD-TDP (annexe 2). Patients were significantly younger at first symptoms in FTLD-TDP compared to FTLD-Tau patients, 57 years vs 62 years (p=0.0077).

There were significatively (p=0,0114) more patients with a behavioural initial presentation in FTLD-TDP (59%) compared to the FTLD-Tau group (35%). No statistically significant difference was found between these two groups concerning the other variables.

The covariates included in the multivariate analysis were: behavioural profile, age of onset, non-semantic aphasia, amnesic presentation, behavioural presentation and disease duration. Multivariate analysis did not confirm a statistically significant difference.

However, these two groups are very heterogenous. Therefore, we performed another bivariate analysis on 5 five different neuropathological subgroups: FTLD-TDP type A/B, FTLD-TDP type C, PSP/CBD, Pick's disease and AGD. Results are presented in table 4.

Table 4. Bivariate analysis on neuropathological subgroups for a clinicopathological correlation with behavioural profiles

	TDP A/B N=41	TDP C N=11	PSP/CBD N=27	Pick N=11	AGD N=11	p. overall
Demographic features						
Women, n (%)	12 (29)	3 (27)	10 (37)	4 (36)	6 (55)	0.5913
Clinical characteristics						
Age at first symptom, m (sd)	57 (8)	61 (6.5)	64 (9.7)	54 (7.1)	69 (6.9)	<0.0001*
Disease duration, m (sd)	9 (6.8)	12 (3.1)	9 (5.3)	12 (4.8)	14 (5.9)	0.0029*
Initial clinical presentation, n (%)						
Behavioral	25 (61)	4 (36)	6 (22)	7 (64)	4 (36)	0.0169*
Non semantic aphasia	5 (12)	2 (18)	9 (33)	2 (18)	1(9)	0.2671
Amnesic	5 (12)	0	4 (15)	0	6 (55)	0.0051*
Motor	5 (12)	0	8 (30)	1 (9)	0	0.0751
Semantic aphasia	1 (2)	5 (46)	0	1 (9)	0	
Behavioral profile, n (%)						0.0372*
Apathy	18 (44)	2 (18)	13 (48)	2 (18)	8 (73)	
Disinhibition	19 (46)	6 (55)	6 (22)	5 (46)	2 (18)	
Apathy and disinhibition	3 (7)	1 (9)	3 (11)	1 (9)	1 (9)	
None	1 (2)	2 (18)	5 (19)	3 (27)	0	
Loss of empathy, n (%)	23 (56)	5 (46)	12 (44)	7 (64)	5 (45)	0.7623
Perseverative behaviour, n (%)	23 (56)	7 (64)	14 (52)	8 (73)	7 (64)	0.8096
Dietary changes, n (%)	27 (64)	8 (73)	14 (52)	6 (55)	6 (55)	0.7384

*n : number, m : mean, sd : standard deviation, ALS : amyotrophic latero-sclerosis, TDP : TAR DNA-binding protein, TDP A/B : FTLD TDP type A or B, TDP C : FTLD TDP type C, TDP U : FTLD-TDP undetermined, Tau : tubulin associated unit, TAU 4R : FTLD-Tau 4R, MAPT : microtubule-associated protein tau , FUS : Fused-in-sarcoma, * : statistically significant difference*

As shown in table 4, this analysis showed a statistically difference regarding age of onset (p<0,0001) and disease duration (p=0,0029). Pick's disease presented symptoms earlier (54 years) than patients with AGD (69 years), mean disease duration was 9 years in FTLD-TDP A/B and PSP/CBD whereas 14 years in AGD.

There was a statistically significant difference in the distribution of behavioural initial clinical presentation (p=0,0169): 7 (64%) Pick's disease, 25 (61%) FTLD-TDP type A/B, 4 (36%) FTLD-TDP type C, 4 (36%) AGD, and 6 (22%) PSP/CBD.

The distribution of amnesic presentations was also statistically significant (p= 0,0051): 6 (55%) AGD, 4 (15%) PSP/CBD, 5 (12%) FTLD-TDP type A/B and no FTLD-TDP type C nor Pick's disease.

Finally, this analysis shows a statistically significant distribution of behavioural profiles (p=0,0372). Eighteen (44%) FTLD-TDP type A/B were described with an apathetic profile and 19 (46%) with disinhibited profile. Six (55%) FTLD-TDP type C were described with disinhibited profile, 2(18%) with apathetic profile and 2(18%) with neither apathetic nor disinhibited profile. Thirteen (48%) PSP/CBD were diagnosed with apathetic profile, every other profile was also described. Five (46%) Pick's disease were described as disinhibited, 3 (27%) of them were neither apathetic nor disinhibited whereas 2 (18%) were described as apathetic. Eight (73%) AGD were described with apathetic profile and 2 (18%) with disinhibition.

With these neuropathological subgroups, multivariate analysis was not possible due to the small sample of patients in each group.

4 Discussion

In this retrospective multicentric study, we described a cohort of 114 patients with *post mortem* confirmed FTLD and we investigated the correlations between 4 different behavioural profiles and the underlying pathology.

Our population had similar characteristics compared to other cohorts of patients with *post mortem* confirmed FTLD: early age of onset <65 years (60 years), female minority (35%), disease duration (10 years) [2,26,40,41]. Forty-three percent of patients had a family history of cognitive impairment, 17% had a genetic mutation [42]. Neuropathological results revealed a majority of FTLD-TDP (49%) versus FTLD-Tau (46%), and a minority of FTLD-FUS (5%) which is also consistent with the literature [7,43,44].

Our study confirms that one initial clinical diagnosis can be associated to different underlying pathologies. Regarding semantic dementia which is described as specific for underlying neuropathology FTLD-TDP type C, 4 (44%) patients had another neuropathological diagnosis (2 FTLD-Tau, 2 FTLD-TDP type A/B) [38].

Additionally, we observed that only half of patients with FTLD-TDP type C were initially diagnosed with a presentation of semantic aphasia, 4 (36%) were described with behavioural presentation and 2 (18%) with non-semantic aphasia.

These findings are consistent with the literature as Perry *et al* described patients with behavioural presentations and FTLD-TDP type C [26]. Moreover, Erkoyun *et al* described that semantic presentation are correlated to left temporal lobe atrophy in contrast with behavioural presentation which are correlated to right temporal lobe atrophy [45].

On the other hand, PSPS is described as very specific for underlying neuropathology PSP, however in our cohort 2 (33%) patients were diagnosed with FTLD-TDP B and had C9orf72 mutation [16,46]. A second analysis of medical records revealed that the patients clinical presentations were only “suggestive” of PSP, according to the clinical diagnostic criteria for PSP of 2017 [16]. Indeed, no vertical supranuclear gaze palsy, repeated unprovoked falls, nor gait freezing were described. The level of diagnostic certainty of suggestive PSP is known to be less specific of neuropathological diagnosis of PSP.

As described in previous studies, CBS and nf-FTD tend to be more correlated to FTLD-Tau, but are not specific for an underlying neuropathology. Likewise, in our cohort, a majority were FTLD-Tau (respectively 86% and 70%) [47].

Concerning bv-FTD, it is usually described as evenly shared between FTLD-Tau and FTLD-TDP. In our study, there was a majority of FTLD-TDP (64%) compared to FTLD-Tau (29%) and FTLD-FUS (7%) [47].

The 23 patients initially diagnosed with Alzheimer’s disease presented any of the neuropathological diagnoses except FTLD-FUS. Amnesic impairment doesn’t seem to suggest one specific diagnosis.

Finally, our findings on FTLD-FUS support previous descriptions. Indeed, patients started symptoms earlier (41 years) than other groups, their disease duration was shorter (6 years), and initial clinical presentation was specifically a behavioural presentation (100%). Patients with FTLD-FUS were always described with disinhibition, alone or associated to apathy. Although, this group of patients involves only 6 patients, our results are consistent with literature [26].

Apathy and/or disinhibition are found in 90% of patients and in every initial clinical presentation. The high prevalence of these 2 symptoms reveals the weight of these aspects of FTD semiology. It supports our questioning on its correlation with the underlying pathology.

Studying their distribution in the different groups of initial presentations enlightened how physicians classify patients. No patients with behavioural presentation was described without apathy or disinhibition, although they are not major Rascovsky's criteria [5].

On the other hand, no patient with motor presentation was described with disinhibition, although, criteria for CBD and PSP both describe patients with early behavioural impairment including disinhibition [15,16,46].

Bivariate analysis revealed that behavioural initial presentation was prominent for FTLD-TDP compared to FTLD-Tau and that patients with FTLD-TDP presented symptoms earlier (58 years) compared to FTLD-Tau (62 years). However, these differences did not remain significant in the multivariate analysis.

In order to minimize bias due to the heterogeneity of each group, we analysed patients according to 5 different neuropathological subgroups (FTLD-TDP type A/B, FTLD type C, PSP/CBD, Pick's disease and AGD).

Bivariate analysis revealed that patients with Pick's disease presented symptoms earlier (54 years) than patients with AGD (69 years), mean disease duration was about 9 years in FTLD-TDP type A/B and PSP/CBD whereas 14 years in AGD.

Behavioural initial clinical presentation represented 2/3 of patients with FTLD-TDP type A/B and Pick's disease, and only 1/3 in other groups. As Perry *et al* described, this clinical presentation alone cannot discriminate patients [26].

On the other hand, amnesic presentations were not described in patients with FTLD-TDP type C nor Pick but in half of patients with AGD. This confirms what was previously described on patients with AGD [48]. However, this clinical presentation is not specific to this neuropathological diagnosis and was also described in 12% of FTLD-TDP type A/B and 15% of PSP/CBD.

FTLD-TDP type C and Pick's disease presented more disinhibited profiles (respectively 6 (55%) and 5 (46%) whereas PSP/CBD and AGD presented more apathetic profiles (respectively 13 (48%) and 8 (73%)), and FTLD-TDP type A/B were equally distributed between apathetic and disinhibited profiles. With these subgroups multivariate analysis was not possible due to the small sample of patients in each group. These correlations reveal trends but unfortunately none is specific and can predict one neuropathological diagnosis.

To our knowledge we present the largest (114 patients) cohort including patients with a *post mortem* confirmed FTLD established with current neuropathological methods. Interview with the patients referring neurologist on every case allowed investigators to minimize interpretative bias while reading medical records.

Our study also has limitations. First, it is a retrospective study, some patients died more than 20 years ago with sometimes few clinical data and difficulties for the referring neurologist to remember details on their patients. We minimized this bias by excluding patients with very few clinical data in the medical record.

We have considered that Rascovsky's criteria were the most appropriate to study behavioral aspects of all FTD patients including language and motor presentations although they were established for patients with bv-FTD.

Regarding the behavioral categorization, we classified patients *a posteriori*, and no uniform scales such as the Neuropsychiatric Inventory [49] or The Frontal Systems Behavior Scale were available in the medical records [50].

To conclude, the description of our cohort is consistent with the literature. Moreover, our study confirms that initial clinical diagnosis fails to predict the underlying pathology. Our statistical analysis revealed that AGD presented most frequently with an amnesic initial clinical presentation and began symptoms older than other neuropathological subgroups. Furthermore, our analysis on apathetic and disinhibited profiles showed that FTLD-TDP type C and Pick's disease presented most frequently with a disinhibited profile whereas AGD and PSP/DCB presented most frequently with an apathetic profile. As we described earlier, apathy and disinhibition seem to be correlated to specific brain atrophy localization [20]. Therefore, we think that further studies using neuropsychological profile, language assessment and functional and morphologic brain imaging could improve clinico-pathological correlation regarding these behavioural profiles.

Conclusion

Cette étude rétrospective multicentrique de patients présentant une dégénérescence lobaire fronto-temporale (DLFT) confirmée post mortem a permis l'étude d'une cohorte de 114 patients. Les caractéristiques de notre population correspondent aux données de la littérature. Notre étude confirme la mauvaise corrélation entre les diagnostics cliniques initiaux posés par les neurologues et les diagnostics neuro-pathologiques réalisés *post mortem*. L'analyse statistique que nous avons menée comparant les sous-groupes neuro-pathologiques en fonction des profils comportementaux, des critères cliniques de Rascovsky, des présentations cliniques initiales et des données démographiques a montré que les DLFT-TDP type C et les maladies de Pick avaient majoritairement un profil désinhibé, les AGD et PSP/DCB avaient majoritairement un profil apathique et les AGD avaient principalement une présentation initiale amnésique. De prochaines études associant les données des bilans neuropsychologiques, orthophoniques et de neuroimagerie pourraient permettre d'affiner les résultats, en attendant le développement de nouveaux biomarqueurs et techniques de neuroimagerie.

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Références

[1] Hendriks S, Peetoom K, Bakker C, van der Flier WM, Papma JM, Koopmans R, et al. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol 2021. https://doi.org/10.1001/jamaneurol.2021.2161.

[2] Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry 2013;25:130–7. https://doi.org/10.3109/09540261.2013.776523.

[3] Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. Br J Psychiatry 2002;180:140–3. https://doi.org/10.1192/bjp.180.2.140.

[4] Lebouvier T, Bertoux M, Leroy M, Lebert F, Deramecourt V, Pasquier F. Diagnostic positif et étiologique des démences frontotemporales. Prat Neurol - FMC 2019;10:101–11. https://doi.org/10.1016/j.praneu.2019.02.012.

[5] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456–77. https://doi.org/10.1093/brain/awr179.

[6] Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–14. https://doi.org/10.1212/WNL.0b013e31821103e6.

[7] Lashley T, Rohrer JD, Mead S, Revesz T. Review: An update on clinical, genetic and pathological aspects of frontotemporal lobar degenerations: Frontotemporal lobar degeneration, a review. Neuropathol Appl Neurobiol 2015;41:858–81. https://doi.org/10.1111/nan.12250.

[8] Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 2015;14:253–62. https://doi.org/10.1016/S1474-4422(14)70324-2.

[9] Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol (Berl) 2010;119:1–4. https://doi.org/10.1007/s00401-009-0612-2.

[10] Mackenzie IRA, Neumann M, Baborie A, Sampathu DM, Plessis DD, Jaros E, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol (Berl) 2011;122:111–3. https://doi.org/10.1007/s00401-011-0845-8.

[11] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016;537:50–6. https://doi.org/10.1038/nature19323.

[12] Masdeu JC. Neuroimaging of Diseases Causing Dementia. Neurol Clin 2020;38:65–94. https://doi.org/10.1016/j.ncl.2019.08.003.

[13] Swift IJ, Sogorb-Esteve A, Heller C, Synofzik M, Otto M, Graff C, et al. Fluid biomarkers in frontotemporal dementia: past, present and future. J Neurol Neurosurg Psychiatry 2021;92:204–15. https://doi.org/10.1136/jnnp-2020-323520.

[14] Meeter LH, Kaat LD, Rohrer JD, van Swieten JC. Imaging and fluid biomarkers in frontotemporal dementia. Nat Rev Neurol 2017;13:406–19. https://doi.org/10.1038/nrneurol.2017.75.

[15] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1.

[16] Hoglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. Mov Disord Off J Mov Disord Soc 2017;32:853–64. https://doi.org/10.1002/mds.26987.

[17] Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. Brain 2011;134:2502–12. https://doi.org/10.1093/brain/awr173.

[18] Powers JP, Massimo L, McMillan CT, Yushkevich PA, Zhang H, Gee JC, et al. White Matter Disease Contributes to Apathy and Disinhibition in Behavioral Variant Frontotemporal Dementia. Cogn Behav Neurol 2014;27:206–14. https://doi.org/10.1097/WNN.0000000000000044.

[19] Borroni B, Benussi A, Premi E, Alberici A, Marcello E, Gardoni F, et al. Biological, Neuroimaging, and Neurophysiological Markers in Frontotemporal Dementia: Three Faces of the Same Coin. J Alzheimers Dis 2018;62:1113–23. https://doi.org/10.3233/JAD-170584.

[20] Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. Neurology 2008;71:736–42. https://doi.org/10.1212/01.wnl.0000324920.96835.95.

[21] Snowden JS. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry 2001;70:323–32. https://doi.org/10.1136/jnnp.70.3.323.

[22] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–54. https://doi.org/10.1212/wnl.51.6.1546.

[23] Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet Lond Engl 2015;386:1672–82. https://doi.org/10.1016/S0140-6736(15)00461-4.

[24] Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta Neuropathol (Berl) 2009;117:15–8. https://doi.org/10.1007/s00401-008-0460-5.

[25] Mackenzie IR, Neumann M. Reappraisal of TDP-43 pathology in FTLD-U subtypes. Acta Neuropathol (Berl) 2017;134:79–96. https://doi.org/10.1007/s00401-017-1716-8.

[26] Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain 2017;140:3329–45. https://doi.org/10.1093/brain/awx254.

[27] Hodges JR, Mitchell J, Dawson K, Spillantini MG, Xuereb JH, McMonagle P, et al. Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases. Brain 2010;133:300–6. https://doi.org/10.1093/brain/awp248.

[28] Snowden J, Neary D, Mann D. Frontotemporal lobar degeneration: clinical and pathological relationships. Acta Neuropathol (Berl) 2007;114:31–8. https://doi.org/10.1007/s00401-007-0236-3.

[29] Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathol (Berl) 2011;122:137–53. https://doi.org/10.1007/s00401-011-0839-6.

[30] The FReJA Consortium, Urwin H, Josephs KA, Rohrer JD, Mackenzie IR, Neumann M, et al. FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. Acta Neuropathol (Berl) 2010;120:33–41. https://doi.org/10.1007/s00401-010-0698-6.

[31] Peters F, Perani D, Herholz K, Holthoff V, Beuthien-Baumann B, Sorbi S, et al. Orbitofrontal Dysfunction Related to Both Apathy and Disinhibition in Frontotemporal Dementia. Dement Geriatr Cogn Disord 2006;21:373–9. https://doi.org/10.1159/000091898.

[32] Robert P, Onyike CU, Leentjens AFG, Dujardin K, Aalten P, Starkstein S, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009;24:98–104. https://doi.org/10.1016/j.eurpsy.2008.09.001.

[33] Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004;56:399–406. https://doi.org/10.1002/ana.20203.

[34] Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain J Neurol 2005;128:1996–2005. https://doi.org/10.1093/brain/awh598.

[35] Shi J, Shaw CL, Du Plessis D, Richardson AMT, Bailey KL, Julien C, et al. Histopathological changes underlying frontotemporal lobar degeneration with clinicopathological correlation. Acta Neuropathol (Berl) 2005;110:501–12. https://doi.org/10.1007/s00401-005-1079-4.

[36] Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006;66:41–8. https://doi.org/10.1212/01.wnl.0000191307.69661.c3.

[37] Lladó A, Sánchez-Valle R, Rey MJ, Ezquerra M, Tolosa E, Ferrer I, et al. Clinicopathological and genetic correlates of frontotemporal lobar degeneration

and corticobasal degeneration. J Neurol 2008;255:488–94. https://doi.org/10.1007/s00415-008-0565-8.

[38] Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain 2011;134:2565–81. https://doi.org/10.1093/brain/awr198.

[39] Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, et al. Frontotemporal dementia: Clinicopathological correlations. Ann Neurol 2006;59:952–62. https://doi.org/10.1002/ana.20873.

[40] Ratnavalli E, Brayne C, Dawson K, Hodges JR. CME The prevalence of frontotemporal dementia n.d.:8.

[41] Ber IL, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Anterion C, et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain 2006;129:3051–65. https://doi.org/10.1093/brain/awl288.

[42] Pottier C, Ravenscroft TA, Sanchez-Contreras M, Rademakers R. Genetics of FTLD: overview and what else we can expect from genetic studies. J Neurochem 2016;138 Suppl 1:32–53. https://doi.org/10.1111/jnc.13622.

[43] Mackenzie IRA, Baborie A, Pickering-Brown S, Plessis DD, Jaros E, Perry RH, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol (Berl) 2006;112:539–49. https://doi.org/10.1007/s00401-006-0138-9.

[44] Sampathu DM, Neumann M, Kwong LK, Chou TT, Micsenyi M, Truax A, et al. Pathological Heterogeneity of Frontotemporal Lobar Degeneration with Ubiquitin-Positive Inclusions Delineated by Ubiquitin Immunohistochemistry and Novel Monoclonal Antibodies. Am J Pathol 2006;169:1343–52. https://doi.org/10.2353/ajpath.2006.060438.

[45] Ulugut Erkoyun H, Groot C, Heilbron R, Nelissen A, van Rossum J, Jutten R, et al. A clinical-radiological framework of the right temporal variant of frontotemporal dementia. Brain 2020;143:2831–43. https://doi.org/10.1093/brain/awaa225.

[46] Irwin DJ. Tauopathies as clinicopathological entities. Parkinsonism Relat Disord 2016;22 Suppl 1:S29-33. https://doi.org/10.1016/j.parkreldis.2015.09.020.

[47] Irwin DJ, Cairns NJ, Grossman M, McMillan CT, Lee EB, Van Deerlin VM, et al. Frontotemporal Lobar Degeneration: Defining Phenotypic Diversity Through Personalized Medicine. Acta Neuropathol (Berl) 2015;129:469–91. https://doi.org/10.1007/s00401-014-1380-1.

[48] Ferrer I, Santpere G, van Leeuwen FW. Argyrophilic grain disease. Brain 2008;131:1416–32. https://doi.org/10.1093/brain/awm305.

[49] Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. Neurology 1997;48:10S-16S. https://doi.org/10.1212/WNL.48.5_Suppl_6.10S.

[50] Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS. Factor Analysis of the Frontal Systems Behavior Scale (FrSBe). Assessment 2003;10:79–85. https://doi.org/10.1177/1073191102250339.

Annexe 1

Distribution of the neuropathological diagnosis among the initial clinical diagnosis

	bv-FTD N=43	sv-FTD N=9	nf-FTD N=10	CBS N=7	PSPS N=6	AD N=23	LBD N=2	PD N=1	VD N=3	psy N=5	Depression N=2
TDP, n (%)											
TDP A/B	22 (52)	2 (22)	3 (30)	1 (14)	2 (33)	7 (30)	1 (50)	1 (100)	0	0	2 (100)
TDP C	2 (5)	5 (56)	0	0	0	3 (13)	0	0	0	0	0
TDP U	3 (7)	0	0	0	0	0	0	0	0	0	0
Tau, n (%)											
Tau 4R	8 (19)	0	6 (60)	4 (57)	4 (67)	11 (48)	1 (50)	0	3 (100)	1 (20)	0
Pick	4 (10)	1 (11)	1 (10)	2 (29)	0	1 (4)	0	0	0	1 (20)	0
MAPT	0	1 (11)	0	0	0	1 (4)	0	0	0	0	0
FUS, n (%)	3 (7)	0	0	0	0	0	0	0	0	3 (60)	0

n : number, m : mean, sd : standard deviation, bv-FTD: behavioural variant of fronto-temporal dementia, sv-FTD : semantic variant of fronto-temporal demantia, nf-FTD : non-fluent variant of fronto-temporal dementia, CBS : corticobasal syndrome, PSPS : progressive supranuclear palsy, AD : Alzheimer's disease, LBD : Lewy Body dementia, PD : Parkinson's disease, VD : vascular dementia, psy : psychiatric disorder, VD: vascular dementia, TDP : TAR DNA-binding protein, TDP A/B : FTLD TDP type A or B, TDP C : FTLD TDP type C, TDP U : FTLD-TDP undetermined, Tau : tubulin associated unit, TAU 4R : FTLD-Tau 4R, MAPT : microtubule-associated protein tau , FUS : Fused-in-sarcoma,

Annexe 2

Bivariate analysis on FTLD-Tau and FTLD-TDP for a clinicopathological correlation with behavioural profile

Histopathological diagnosis	**TAU (n=52)**	**TDP (n= 56)**	**p value**
Demographic features			
Women, n (%)	20 (39)	18 (32)	0.4920
Clinical characteristics			
Age at first symptom, m (sd)	62.2 (10)	57.6 (8)	0.0077*
Disease duration, m (sd)	10.9 (6)	9.4 (6)	0.1683
Initial clinical presentation, n (%)			
Behavioral	18 (35)	33 (59)	0.0114*
Non semantic aphasia	12 (23)	7 (13)	0.1492
Amnesic	11 (21)	5 (9)	0.0739
Motor	9 (17)	5 (9)	0.2553
Semantic aphasia	2 (4)	6 (11)	0.2731
Behavioral profile			0.0614
Apathy	25 (48)	20 (36)	
Desinhibition	14 (27)	28 (50)	
Apathy and desinhibition	5 (10)	5 (9)	
None	8 (15)	3 (5)	
Other Rascovsky's criteria			
Loss of empathy	27 (52)	30 (54)	0.8639
Perseverative, stereotyped behaviour	31 (60)	33 (59)	0.9421
Hyperorality and dietary changes	28 (54)	37 (66)	0.2392

*n : number, m : mean, sd : standard deviation, ALS : amyotrophic latero-sclerosis, TDP : TAR DNA-binding protein, TDP A/B : FTLD TDP type A or B, TDP C : FTLD TDP type C, TDP U : FTLD-TDP undetermined, Tau : tubulin associated unit, TAU 4R : FTLD-Tau 4R, MAPT : microtubule-associated protein tau , FUS : Fused-in-sarcoma, * : statistically significant difference*

AUTEUR : FRANCOIS Grâce
Date de Soutenance : 17/09/2021
Titre de la Thèse : Etude d'une cohorte française de patients présentant une dégénérescence lobaire fronto-temporale confirmée *post mortem*. Analyse des corrélations clinico-pathologiques de leurs profils comportementaux.
Thèse - Médecine - Lille 2021
DES : Neurologie
Mots-clés : dégénérescence lobaire fronto-temporale ; corrélation clinico-pathologique ; apathie ; désinhibition

Résumé :

Contexte : Les dégénérescences lobaires fronto-temporales (DLFT) constituent un groupe hétérogène de maladies neurodégénératives. La prédiction de la nature des lésions neuro-pathologiques sous-jacentes reste difficile du vivant des patients. Cette étude a pour objectif de décrire une population française de patients présentant une DLFT confirmée *post mortem* et d'étudier la corrélation entre le diagnostic neuro-pathologique et le profil comportemental, apathique et/ou désinhibé des patients.

Matériel et Méthodes : Nous avons recensé les patients présentant une DLFT confirmée post mortem entre 1993 et 2021 auprès de 5 Centres de mémoire de ressources et de recherche (CMRR) en France. Nous avons collecté rétrospectivement leurs données cliniques, neuro-pathologiques et génétiques. Nous avons ensuite réalisé une comparaison par sous-groupes neuro-pathologiques (TDP A/B, TDP C, PSP/DCB, Pick, AGD) concernant les données démographiques, les présentations cliniques initiales, les profils comportementaux et les critères cliniques de Rascovsky.
Résultats : 114 patients ont été inclus, il y avait 35% de femmes, l'âge moyen de début était de 60 ans et la durée moyenne d'évolution de la maladie était de 10 ans, 17% avait une mutation génétique. Il y avait 49% de DLFT-TDP, 46% de DLFT-Tau et 5% de DLFT-FUS. Nous avons comparé les 5 sous-groupes neuro-pathologiques, il y avait une différence significative concernant l'âge de début des symptômes ($p<0,0001$), la durée d'évolution de la maladie ($p=0,0029$), la présentation comportementale ($p=0,0169$) et mnésique ($p=0,0051$) initiale et les profils comportementaux ($p=0,0072$).
Conclusion : Les caractéristiques de notre population correspondent aux données de la littérature. Notre étude confirme la mauvaise corrélation entre les diagnostics cliniques initiaux et neuro-pathologiques. L'analyse statistique que nous avons menée comparant les sous-groupes neuro-pathologiques en fonction des profils comportementaux, des présentations cliniques initiales et des données démographiques a montré que les DLFT-TDP type C et les maladies de Pick avaient majoritairement un profil désinhibé, les AGD et PSP/DCB avaient majoritairement un profil apathique et les AGD avaient principalement une présentation initiale amnésique. De prochaines études associant les données de bilans neuropsychologiques, orthophoniques et de neuroimagerie pourraient permettre d'affiner les résultats, en attendant le développement de nouveaux biomarqueurs et de nouvelles techniques de neuroimagerie.

Composition du Jury :

Président : Madame le Professeur Florence Pasquier

Assesseurs : Madame le Docteur Marie-Anne Mackowiak
Monsieur le Docteur Thibaud Lebouvier
Monsieur le Professeur Vincent Deramecourt
Monsieur le Docteur François Sellal