Sex-related differences in the clinical diagnosis of frontotemporal dementia

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ABSTRACT

Objective: To investigate the sex-related differences in the clinical diagnosis of the frontotemporal dementia (FTD) in the Hospital Sant Pau, Barcelona.

Methods: We selected patients diagnosed of FTD from the SPIN cohort (Hospital Sant Pau) and analyzed clinical data. Participants were classified in three different groups according to the clinical presentation. We compared clinical data between sexes in each group.

Results: A total of 193 patients were included: 41% in the behavioural group, 47% in the motor group and 12% in the language group. We found a higher proportion of men in the behavioural group when compared to the motor and language groups (χ-squared=27.042; p<0.001). Within the behavioural group: women presented with a lower MMSE at diagnosis (Mann-Whitney U=262.0; p=0.041) and women received a previous diagnosis of depression more frequently than men (χ-squared= 7.393; p=0.007). In the motor and language groups no sex-related differences were observed.

Conclusions: We observed sex-related differences in the diagnosis of FTD that were restricted to behavioural presentation group.

***Key words*:** frontotemporal dementia; behavioural variant; diagnosis; sex-related differences.

RESUMEN

Objetivo: Investigar las diferencias relacionadas con el sexo en el diagnóstico clínico de la demencia frontotemporal (DFT) en el Hospital Sant Pau, Barcelona.

Material y método: Se seleccionaron pacientes con diagnóstico de DFT de la cohorte SPIN (Hospital Sant Pau) y se analizaron los datos clínicos. Los participantes se clasificaron en tres grupos de acuerdo con la presentación clínica. Se compararon los datos clínicos entre los sexos de cada grupo.

Resultados: Se incluyeron 193 pacientes: 41% en el grupo conductual, 47% en el grupo motor y 12% en el grupo lingüístico. Se encontró una mayor proporción de hombres en el grupo conductual en comparación con los grupos motor y del lenguaje (χ-squared=27.042; $p<0.001$). En el grupo conductual: las mujeres presentaron un MMSE más bajo en el momento del diagnóstico (Mann-Whitney U=262.0; p=0.041) y recibieron un diagnóstico previo de depresión con mayor frecuencia que los hombres (χ-squared= 7.393; p=0.007). En los grupos motor y del lenguaje no se observaron diferencias relacionadas con el sexo.

Conclusiones: En este estudio observamos diferencias relacionadas con el sexo en el diagnóstico de DFT que se limitaron al grupo de presentación conductual.

***Palabras clave*:** demencia frontotemporal; variante conductual; diagnóstico; diferencias de sexo.

RESUM

Objectiu: Investigar les diferències relacionades amb el sexe en el diagnòstic clínic de la demència frontotemporal (DFT) a l'Hospital Sant Pau, Barcelona.

Material i mètode: Es van seleccionar pacients amb diagnòstic de DFT de la cohort SPIN (Hospital Sant Pau) i es van analitzar les dades clíniques. Els participants es van classificar en tres grups d'acord amb la presentació clínica. Es van comparar les dades clíniques entre els sexes de cada grup.

Resultats: Es van incloure 193 pacients: 41% en el grup conductual, 47% en el grup motor i 12% en el grup lingüístic. Es va trobar una major proporció d'homes en el grup conductual en comparació amb els grups motor i de llenguatge (χ-squared=27.042; p<0.001). Al grup conductual: les dones van presentar un MMSE més baix al moment del diagnòstic (Mann-Whitney U=262.0; p=0.041) i van rebre un diagnòstic previ de depressió amb major freqüència que els homes (χ-squared= 7.393; p=0.007). Als grups motor i del llenguatge no es van observar diferències relacionades amb el sexe.

Conclusions: En aquest estudi observem diferències relacionades amb el sexe en el diagnòstic de DFT que es van limitar al grup de presentació conductual.

Paraules clau: demència frontotemporal; variant conductual; diagnòstic; diferències de sexe.

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1. Research question

Our aim was to study the sex-related differences in the diagnosis of the main frontotemporal dementia (FTD)-related syndromes (behavioural, language and motor presentation). We carried out a cross-sectional study to answer the following questions: (i) Are there sex-related differences in the diagnosis of any of the clinical presentations of FTD? (ii) Are there sex-related differences in the frequency of previous psychiatric diagnoses across the clinical presentations of FTD? (iii) Are there sex-related differences in the clinical stage of FTD (as measured by the MMSE) at diagnosis across the different clinical presentations of FTD?

2. Background

Introduction

Frontotemporal Dementia is characterized by the degeneration of the frontal and/or temporal lobes and encompasses multiple clinical syndromes. Patients can be subclassified according to the predominant symptoms at disease onset: (i) prominent behavioural symptoms, (ii) prominent motor impairment, (iii) or a progressive language impairment.

First, the patients with a prominent behavioural syndrome fit into the clinical label of the behavioural variant of FTD (bvFTD). The bvFTD is characterized by a prominent personality change with relative preservation of memory, perception, visuospatial skills and praxis. Although clinical symptoms at diagnosis are variable, they often include prominent behavioural change including symptoms such as: disinhibition (usually with impairment of social behaviour), impulsivity (including careless decisions), apathy (or lack of motivation to engage previously rewarding activities), lack of empathy, change in eating behaviour and cognitive symptoms related to executive dysfunction. The clinical criteria for the diagnosis of the bvFTD have shown good diagnostic accuracy in a large multicenter cohort of patients with pathology-proven FTD (1). Moreover, current diagnostic criteria allow the use of biomarkers to

increase diagnostic certainty (2) and define two categories: possible bvFTD, more sensitive but less specific; and highly probable bvFTD, less sensitive but more specific.

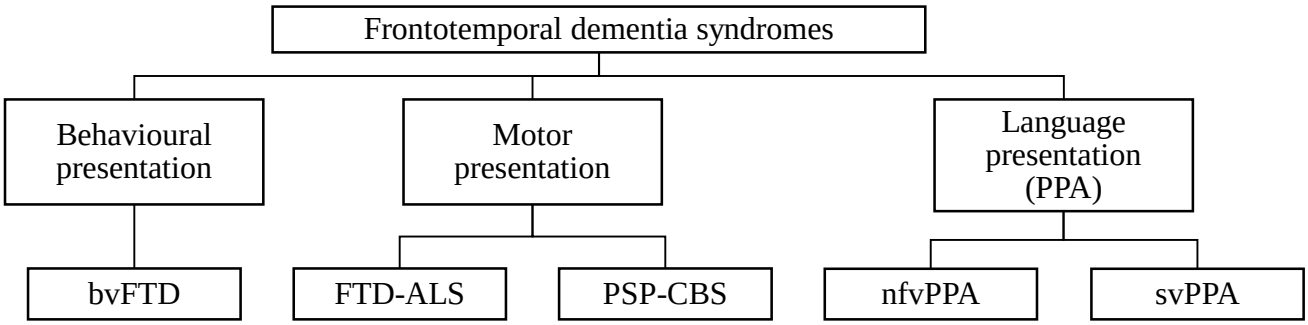
Patients with the bvFTD are often misdiagnosed with psychiatric disorders because neuropsychiatric symptoms of the bvFTD are easily mistaken for those of a primary psychiatric disorder. Thus, the diagnosis of bvFTD presents a special challenge in terms of differential diagnosis with female patients at highest risk for misdiagnosis (3,4).

Another group of patients display prominent motor symptoms at presentation. This group of patients include patients within the FTD-Amyotrophic Lateral Sclerosis continuum (FTD-ALS) and the Progressive Supranuclear Palsy-Corticobasal Degeneration continuum (PSP-CBD). Between 10% and 25% of patients with ALS (characterized by progressive muscle wasting, hyperreflexia, and spasticity) present with FTD clinical phenotypes (progressive aphasia, language impairment, and executive dysfunction) forming the FTD-ALS continuum. On the other hand, patients within the PSP-CBD continuum share motor features such as extrapyramidal symptoms, stiffness and bradykinesia combined with behavioural, motor, and language symptoms.

Finally, a third group of patients display prominent language impairment at presentation. These patients are classified within the clinical umbrella of primary progressive aphasia (PPA). The PPA can be further subclassified into two FTD-related subgroups according to the current diagnostic criteria: the semantic variant [svPPA] and the nonfluent variant [nfvPPA]) (5). Patients with svPPA have a variety of language difficulties, including naming difficulties, impaired understanding of word meaning, and use of substitute words. However, speech is fluent and there is preservation of other cognitive domains. Conversely, patients with nfvPPA show effortful speech with syntactic impairment and preservation of semantic knowledge. Speech output becomes increasingly difficult and in the later stages the patient may become mute.

All these clinical syndromes are included in the umbrella term FTD, as they share a partially-overlapping pattern of neurodegeneration across frontotemporal structures.

Figure 1: Predominant clinical phenotypes of FTD.



Key: bvFTD = behavioural variant of frontotemporal dementia; FTD-ALS = frontotemporal dementia – amyotrophic lateral sclerosis continuum; PSP-CBD= progressive supranuclear palsy – corticobasal degeneration continuum; nfvPPA = nonfluent variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia.

Epidemiology

FTD is a common cause of degenerative dementia, especially among young patients, second only to Alzheimer disease (AD) (6). His prevalence ranges from 15 to 22 per 100,000 persons (7). FTD has been classically described as early-onset dementia (age <65 years) compared to other dementias (8,9), but it is more prevalent among 60-69 and only 13% have an onset before age 50 (10). Younger onset may be due in part to heavy genetic loading for FTD, with up to 50% of cases being familial and up to 40% autosomal-dominant in nature (10).

Sex differences in prevalence have been reported with a 3-to-4.7–fold greater prevalence in males than in females (11,12) although this sex distribution has not been supported by all studies (13,14) and the existence of sex-related differences in the diagnosis of FTD syndromes remain controversial. Importantly, some studies have reported sex-related differences in the diagnosis of some of the FTD clinical subgroups, such as the bvFTD patients, but not in language of motor presentations (15).

Diagnosis

The diagnosis of FTD requires a thorough history, including a detailed family history of dementia, and physical examination. It is particularly important to dissect the timing and rate of progression of symptoms, and behavioural and personality changes over the previous months or years. Clinical

presentation varies across FTD syndromes (**Table 1**). Clinical consensus criteria for diagnosing FTD syndromes have been recently updated (1,5,16–19). Neuroimaging and cerebrospinal fluid (CSF) biomarkers are included in the diagnosis criteria and they are helpful in the diagnosis and excluding other aetiologies.

Mini-Mental State Examination (MMSE) is a simply score commonly used in dementia screening in clinical practice. It has recently demonstrated to be a sensitive index of disease progression in bvFTD (20).

Table 1: Frequency of features of frontotemporal dementia syndromes and Alzheimer disease. Modified from Cardarelly R. *et al* (21).

	Frontotemporal dementia syndromes					
	Behavioural	**Motor**		**Language**		
Relative frequency of syndrome features	**bvFTD**	**FTD-ALS**	**PSP-CBS**	**nfvPPA**	**svPPA**	**AD**
Behavioural or personality changes	+++	+++	++	+	++	+
Extrapyramidal features	+		+++	++	+	+
Rigidity, bradykinesia	+	+	+++	++		
Loss of object knowledge and comprehension deficits	+	++		++	+++	+
Effortful speech, agrammatism, telegraphic speech	+	++	++	+++	+	+
Memory loss	+	+	+	++	++	+++

Key: bvFTD = behavioural variant of frontotemporal dementia; FTD-ALS= frontotemporal dementia – amyotrophic lateral sclerosis continuum; PSP-CBS continuum = progressive supranuclear palsy – corticobasal degeneration continuum; nfvPPA = non-fluent variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; AD = Alzheimer disease.

Treatment

There is no specific cure for FTD; treatment is focused on symptom management and support for patients, families, and caregivers (22). However, disease-modifying treatments for FTD are expected to be developed (23). An accurate clinical diagnosis will be essential for the selection of participants in future clinical trials. Nonetheless, we should take into account the existence of sex-related biases in FTD diagnosis that might hamper the treatment of some patients (24).

Prognosis

There is limited research on the prognosis of FTD. In a retrospective longitudinal in 2005 (25), median survival was 8.7 years (±1.2 years) in patients with FTD compared with 11.8 years (±0.6 years) in

patients with Alzheimer disease. Survival after diagnosis has been previously demonstrated independent of sex by some studies (4) but not all studies support that result and data remains controversial (24).

3. Justification

FTD is the second leading cause of early-onset dementia, and its economic burden is substantial (26). One of the key factors to this burden may be the earlier age at onset, typically occurring during patients' or caregivers' peak earning years. Some studies have suggested that patients with bvFTD are frequently misdiagnosed as having a psychiatric disorder, specially in women (15). The identification of sex-related biases for the diagnosis of bvFTD is essential to improve the recognition of this disease by physicians (24). This would become particularly important when disease modifying treatments become available. However, previous studies assessing sex-related differences in the diagnosis of the bvFTD are scarce and no previous studies have studied sex-related differences in the diagnosis of all the clinical syndromes within the FTD clinical umbrella (that mean including the behavioural, language and motor presentations).

4. Hypotheses and objectives

We hypothesized that there may be sex-related differences in the diagnosis across the main clinical presentations of FTD (behavioural, language and motor). Specifically, we hypothesized that sex-related differences in the diagnosis of FTD may be restricted to the bvFTD group. These differences may be related to social factors influencing the diagnosis of psychiatric and neurodegenerative diseases in middle-aged and older adults. Consequently, women with bvFTD may be misdiagnosed with a psychiatric diagnosis more frequently than men and thus, they might be diagnosed with bvFTD at a more advanced stage.

The specific questions that we wanted to answer in our study were: (i) Are there sex-related differences in the diagnosis of any of the clinical presentations of FTD? (ii) Are there sex-related differences in

the frequency of previous psychiatric diagnoses across the clinical presentations of FTD? (iii) Are there sex-related differences in the clinical stage of FTD (as measured by the MMSE) at diagnosis across the different clinical presentations of FTD?

5. Material and methods

A cross-sectional descriptive design with patients with FTD diagnosis in the Sant Pau Initiative on Neurodegeneration (SPIN cohort: https://santpaumemoryunit.com/our-research/spin-cohort/) from 2010 to 2017 was performed. Data were collected from the electronic database. A time line was performed to guarantee the development of the study (ANNEX 1)

Participants and study design

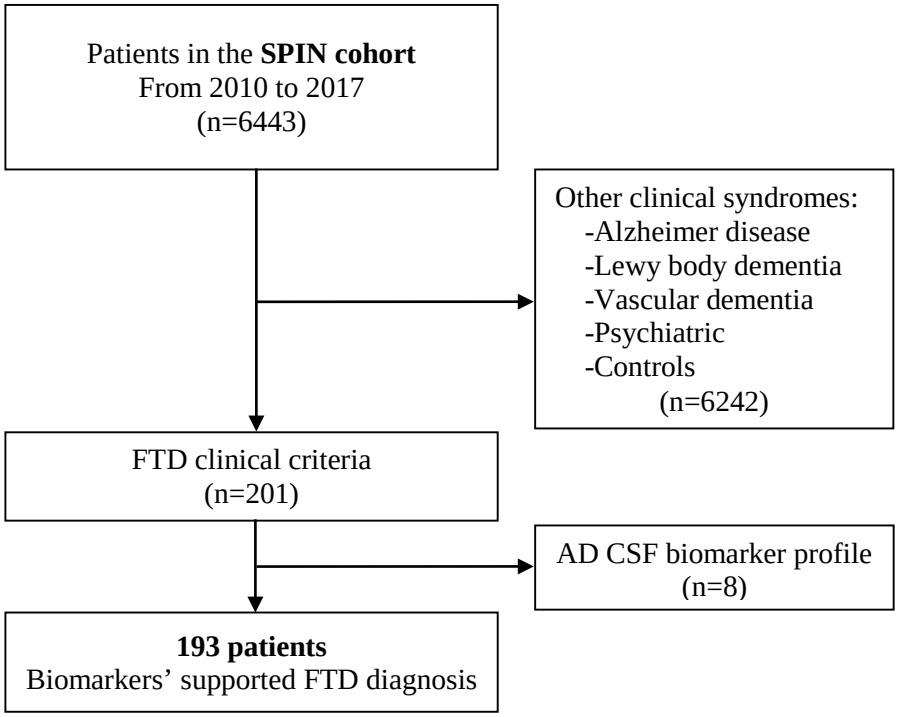
In the SPIN cohort, patients were recruited between January 2010 and December 2017 at the Memory Unit at Hospital Sant Pau (Barcelona, Spain) as part of the cohort. Briefly, patients underwent a uniform set of clinical, neuropsychological, neuroimaging, and laboratory assessments, including CSF sampling. Subjects were referred by general physicians or neurologists because of cognitive or behavioural complaints. All the patients included in the SPIN cohort (**Figure 2**) were screened to fit the eligible inclusion criteria for participation:

1. FTD diagnosis: bvFTD (1), svPPA (5), nfvPPA (5), PSP (16), CBS (21) or ALS (18,19).
2. MMSE at diagnosis.
3. CSF with biomarkers.

The exclusion criterion was AD pathophysiology: CSF t-tau/Aß1-42 ratio > 0.52 (27).

In order to simplify the analysis, patients were grouped into behavioural presentation (bvFTD), language presentation (svPPA and nfvPPA) and motor presentation (ALS, PSP and CBS). Patients with bvFTD were evaluated firstly as a single group and then they were separated on two subgroups based on Rascovsky criteria (1): possible and highly probable bvFTD.

Figure 2: Flow chard of the study patients.



CSF analysis

Availability of CSF was required for the inclusion in the study. All biomarkers were analyzed at the Sant Pau Memory Unit Laboratory with commercially available enzyme-linked immunosorbent assay (ELISA) kits determining levels of Aβ1-42 (Innotest β-amyloid 1-42; Fujirebio Europe) and t-Tau (Innotest hTAU Ag, Fujirebio-Europe) following previously reported methods and manufacturer's instructions (27–29).

Variables of interest

The clinical characteristics were collected prospectively at the time of diagnosis using a homogenized questionnaire for the whole SPIN cohort. Study variables were selected from the electronic database of the SPIN cohort. We selected the MMSE (ANNEX 2) as it has proved to be a simple and reliable measure of the general cognitive impairment in patients with FTD (20). We also studied the presence of the different behavioural symptoms considered in the bvFTD criteria to assess the behavioural profile of each patient (ANNEX 3) (1), the presence of previous psychiatric history (depression, bipolar and psychotic) and familiar history of neurodegenerative disease. Age of onset was the age of

the patient when the earliest symptom of dementia was noted by the patient or carers and it was retrieved during the first visit to our center. Time to diagnosis was defined as the difference between age at which an FTD-related syndrome was diagnosed and age of onset using data from the electronic database.

Statistical analysis

The categorical demographic characteristics of the participants were presented according to frequency and percentage, and the median was used for the continuous variables due to a skewed nature. We used non-parametric test because the variables MMSE and time to diagnosis showed no normality in Kolmogorov-Smirnov test ($D=0.251$, $p<0.001$ and $D=0.169$, $p<0.001$ respectively) and the number of participants in the language group was inferior to 30. In order to compare the differences between sexes, a χ-squared test was used for categorical variables and the Mann-Whitney U test was used for testing the continuous variables. A Pearson correlation coefficient for the correlation between time from onset to diagnosis and MMSE was calculated. A p-value less than 0.05 was defined as statistically significant. All computations and graphics were performed with use of SPSS-IBM (ver. 23).

Ethical considerations.

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent (ANNEX 4) to participate in the study.

Diffusion mechanisms

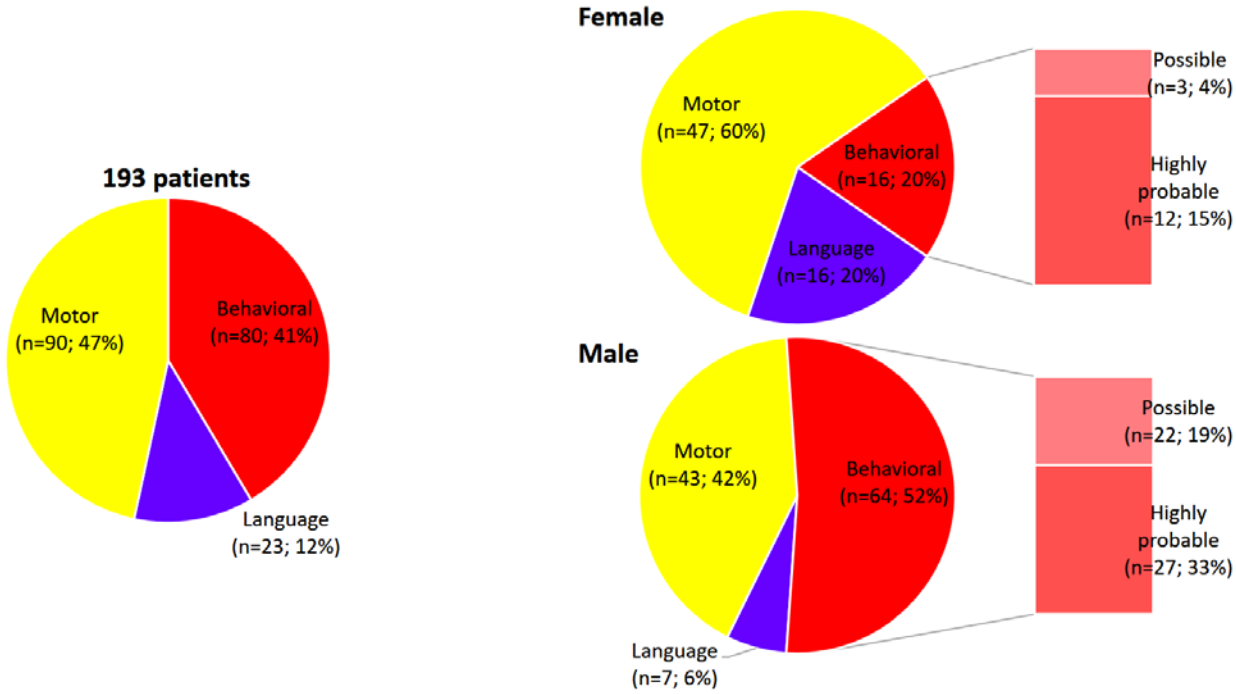
The main diffusion mechanism planned for this investigation is the publication of the study in the *European Journal of Neurology* (Q1, IF:3.956), one of the leading journals in the field of clinical neurology in Europe. Publication in other scientific journals may also be contemplated, especially those concerning specifically clinical neurology in Spain. These include: *Neurologia* (Q3, IF:2.103) and *Revista de Neurologia* (Q3, IF:0.743).

6. Results

Sample composition

We included a total of 193 patients, 79 (40.9%) females and 114 (59.1%) males, with FTD (**Figure 3**, **Table 2**): 80 (41.4%) with bvFTD, 90 (46.6%) with motor presentation and 23 (12%) with language presentation.

Figure 3: Distribution of the FTD-related syndromes in the SPIN cohort.



Patients' characteristics

A) Main clinical diagnosis in each FTD group.

Behavioural and Motor presentations were the commonest presentations. bvFTD was the second presentation in frequency with also two thirds of the patients classified in the high probability group (**Table 4**). Within the motor presentation group, most of the patients belonged to the FTD-ALS continuum. Language was the less common presentation, involving mostly nfvPPA, and with a high percentage of women.

B) Demographic and clinical differences between the FTD groups.

Table 2 summarizes the demographic and clinical differences between clinical groups based on clinical features at presentation.

We observed a higher frequency of men in the bvFTD group when compared to the motor and language groups (χ-squared=27.042; p<0.001). When we separated the bvFTD group in possible and highly probable subgroups using Rascovsky criteria we found a male predominance in both subgroups (χ-squared=11.645, p=0.001; χ-squared=6.897, p=0.009 respectively). The MMSE score at diagnosis was lower and the time from symptom onset to diagnosis was higher in the bvFTD when compared to motor and language groups (Mann-Whitney U=2905.5, p=0.019; Mann-Whitney U=3423.5, p=0.004, respectively). Conversely, the age at symptom onset was similar between groups (Mann-Whitney U=4432.0; p=0.818).

Table 2: Clinical data of the patients included.

	Behavioural presentation	**Motor & Language presentations**	p-value
N (% of total sample)	80 (41.4)	113 (58,6)	
Women	16 (20.0)	63 (55,7)	p<0.001*
Age at onset, y	64.2 (9.9)	66.0 (11.8)	p=0.818
MMSE at diagnosis	25 (6.2)	27 (5.9)	p=0.019*
Time to diagnosis, y	3.7 (3.4)	2.5 (3.4)	p=0.004*
Phenotypes, n			
-Possible	25 (33.8)	-	
-Highly probable	49 (66.2)	-	
-FTD-ALS continuum	-	71 (62.8)	
-FTD-CBD continuum	-	19 (16.8)	
-nfvPPA	-	16 (14.2)	
-svPPA	-	7 (6.2))	

Quantitative variables are shown as median (standard deviation). Categorical variables are described with the number of subjects and the relative frequency (%). *= significant differences (p<0.05). **Key:** MMSE = mini-mental state examination; nfvPPA = nonfluent variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; FTD-ALS continuum = frontotemporal dementia – amyotrophic lateral sclerosis continuum; PSP = progressive supranuclear palsy; CBS = corticobasal syndrome.

Clinical characteristics by sex

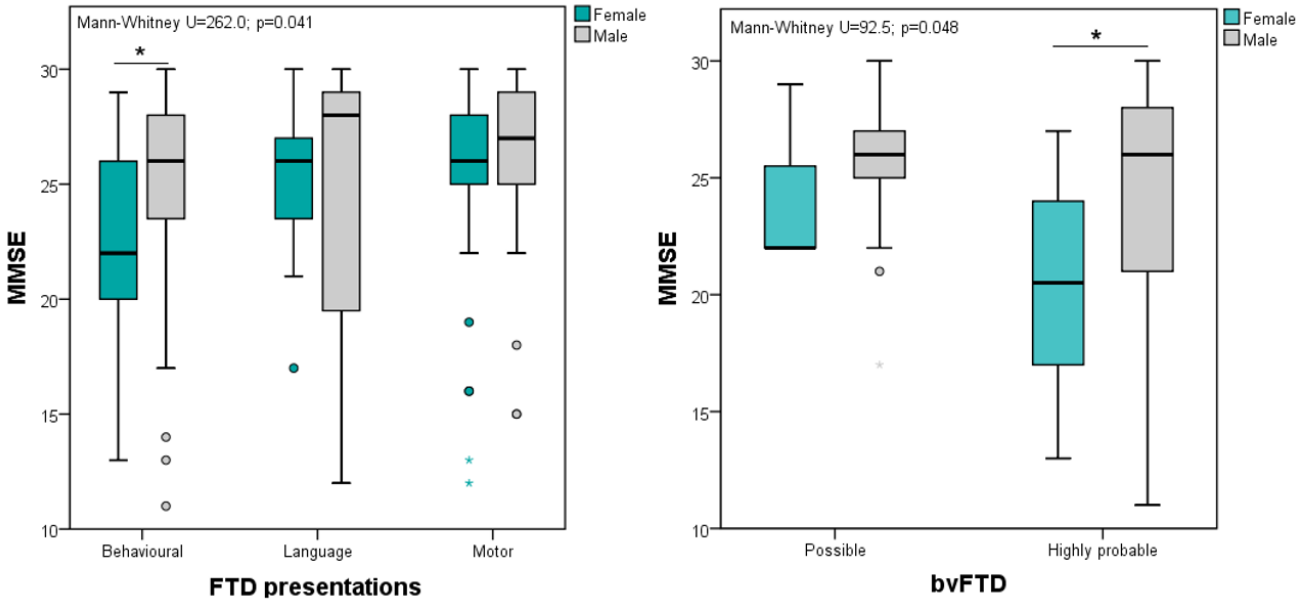
In the behavioural presentation the age of onset showed no differences related to sex. When we compared the severity of presentation at diagnosis, female MMSE was lower (Mann-Whitney U=262.0; p=0.041) than male (Figure 4A). The behavioural profile showed no sex-related differences.

The overall psychiatric history also showed no significant differences. But separating patients by specific psychiatric diagnosis, women with bvFTD received a depression diagnosis more often (χ-squared= 7.393; p=0.007) than men in the same group (**Table 3**). Family history of neurodegeneration showed no influence by sex in any of the three presentations. The time from the onset of symptoms to diagnosis was no different between the sexes. To better understand the relationship between the time and the MMSE we analyzed the relationship between both variables, but the time was not correlated with a worse MMSE in either women or men (r=0.003, p=0.443; r=-0.098, p=0.003 respectively).

To obtain a purer sample of bvFTD patients, we separated patients using biomarkers (**Table 4**). The possible subgroup may be contaminated by psychiatric patients. In contrast, the highly probable subgroup has a purer diagnosis. In the highly probable subgroup we found lower MMSE (**Figure 4B**) and higher depression diagnosis (Mann-Whitney U=92.5, p=0.048; χ-squared= 8.361, p=0.004 respectively) in women.

The motor and language presentations showed no sex-related differences in any of the clinical data analyzed.

Figure 4: Sex differences in MMSE of: A) FTD presentations, B) behavioural presentation.



Key: MMSE= mini-mental state examination, FTD = frontotemporal dementia, bvFTD= behavioural presentation, *= p<0.05.

Table 3: Sex differences in the three FTD presentations.

	Behavioural presentation N=80 (41.4%)			**Motor presentation N=90 (46.6%)**			**Language presentation N=23 (12%)**		
	Female 16 (20.0%)	Male 64 (80.0%)	p-value	Female 47 (52.2%)	Male 43 (47.8%)	p-value	Female 16 (69.6%)	Male 7 (30.4%)	p-value
Age of onset, y	64.4 (8.8)	64.0 (10.2)	0.493	67.5 (12.2)	61.9 (12.5)	0.080	66.5 (7.5)	63.7 (10.3)	0.548
MMSE, /30	22.0 (4.4)	26.0 (5.0)	0.041*	26.0 (5.2)	27.0 (3.9)	0.194	26.0 (5.5)	28.0 (10.6)	0.368
Behavioural profile, n									
- Disinhibition	14 (87.5)	58 (90.6)	0.709	15 (31.9)	7 (16.3)	0.085	4 (25.0)	2 (28.6)	1.000
- Apathy	14 (87.5)	52 (81.3)	0.556	13 (27.7)	7 (16.3)	0.195	9 (56.3)	2 (28.6)	0.371
- Empathy	11 (68.8)	46 (71.9)	0.805	6 (12.8)	6 (14.0)	0.869	0 (0)	0 (0)	-
- Ritual	12 (75.0)	44 (68.8)	0.626	6 (12.8)	6 (14.0)	0.869	1 (6.3)	0 (0)	1.000
- Food oral	12 (75.0)	44 (68.8)	0.626	6 (12.8)	3 (7.0)	0.489	1 (6.3)	1 (14.3)	0.526
- Executive	5 (31.3)	30 (46.9)	0.260	23 (48.9)	18 (41.9)	0.501	6 (37.5)	3 (42.9)	1.000
Psychiatric history, n	9 (56.3)	20 (31.3)	0.063	16 (34.8)	9 (20.9)	0.146	5 (35.7)	1 (16.7)	0.613
- Depression	10 (62.5)	17 (26.6)	0.007*	16 (34.8)	8 (18.6)	0.086	6 (40.0)	0 (0)	0.260
- Bipolar	1 (6.7)	3 (4.7)	0.753	0 (0)	1 (2.3)	1.000	0 (0)	1 (16.7)	0.300
- Psychotic	2 (13.3)	2 (3.2)	0.165	1 (2.1)	0 (0)	0.089	14 (87.5)	5 (71.4)	0.557
Familiar history, n	6 (37.5)	33 (52.4)	0.288	14 (34.1)	11 (26.8)	0.472	8 (50.0)	2 (40.0)	1.000
Time to diagnosis, y	4.3 (2.2)	3.6 (3.7)	0.918	2.3 (3.0)	3.2 (4.2)	0.315	2.0 (2.3)	3.2 (1.41)	0.249

Quantitative variables are shown as median (standard deviation). Categorical variables are described with the number of subjects and the relative frequency (%). *= significant differences (p<0.05). **Key:** MMSE = mini-mental state examination.

Table 4: Characteristics in bvFTD grouped in possible and highly probable diagnostic subgroups using Rascovsky criteria.

	Possible bvFTD N=25 (33.8%)			**Highly probable bvFTD N=49 (66.2%)**		
	Female 3 (12%)	Male 22 (88%)	p-value	Female 12 (24.5%)	Male 37 (75.5%)	p-value
Age of onset, y	66.8 (7.2)	66.6 (10.4)	0.676	62.0 (9.9)	62.6 (9.9)	0.727
MMSE, /30	22.0 (4.0)	26.0 (2.9)	0.499	21.0 (4.4)	26.0 (5.9)	0.048*
Behavioural profile, n						
- Disinhibition	2 (66.7)	19 (86.4)	0.422	12 (100)	35 (94.6)	1.000
- Apathy	3 (100)	20 (90.9)	1.000	11 (91.7)	28 (75.7)	0.237
- Empathy	2 (66.7)	15 (68.2)	1.000	9 (75.0)	29 (78.4)	0.232
- Ritual	2 (66.7)	14 (63.6)	1.000	10 (83.3)	29 (78.4)	0.711
- Food oral	2 (66.7)	15 (68.2)	1.000	10 (83.3)	26 (70.3)	0.373
- Executive	1 (33.3)	14 (63.6)	0.543	4 (33.3)	15 (40.5)	0.656
Psychiatric history, n	2 (66.7)	6 (27.3)	0.231	7 (58.3)	12 (32.4)	0.110
- Depression	2 (66.7)	7 (31.8)	0.530	8 (66.7)	8 (21.6)	0.004*
- Bipolar	0 (0)	2 (9.1)	1.000	1 (9.1)	1 (2.7)	0.410
- Psychotic	1 (33.3)	1 (4.5)	0.230	1 (9.1)	1 (2.8)	0.417
Familiar history, n	1 (33.3)	11 (50.0)	1.000	4 (33.3)	18 (50.0)	0.316
Time to diagnosis, y	5,0 (2.4)	3.8 (4.9)	0.065	3.5 (2.0)	3.6 (3.0)	0.561

Quantitative variables are shown as median (standard deviation). Categorical variables are described with the number of subjects and the relative frequency (%). *= significant differences (p<0.05). **Key:** MMSE = mini-mental state examination.

7. Discussion

We report sex-related differences in the clinical diagnosis of the bvFTD in a large sample of FTD patients from a referral center of neurodegenerative dementias in Catalonia. Importantly, the observed sex-related differences were restricted to the bvFTD. In the bvFTD, women showed a higher frequency of previous psychiatric diagnosis when compared to men. This finding may suggest that women that are diagnosed of bvFTD in our environment receive a previous psychiatric diagnosis more frequently than men. Furthermore, we found lower MMSE at diagnosis in women diagnosed of bvFTD when compared to men. This finding may suggest that women that are finally diagnosed of bvFTD may be referred to our centre at a later disease stage than men. These results underscore a possible bias towards the misdiagnosis of psychiatric illness in the bvFTD, as suggested by a previous study in the United States of America (15).

In our cohort, we found a male predominance restricted to the bvFTD. Then, we analyzed that group using biomarkers classification according to Rascovsky criteria. The proportion of possible bvFTD and highly probable bvFTD was similar to the observed in previous well-characterized cohorts (30). In booth subgroups (possible and highly probable bvFTD) we found a male predominance. Finally, we found a similar behavioural profile in men and women. Thus, we did not find sex-related differences in the phenotype of the bvFTD in our center. Taken together, these findings suggest a sex-related bias in the identification of bvFTD before the referral of the patients to our center.

It is worth noting that bvFTD symptoms may mimic psychiatric symptoms, leading to psychiatric misdiagnosis (3,4). Family members and doctors that are not familiar with the diagnosis of the bvFTD may overlook the typical change in personality of patients with the bvFTD and misdiagnose bvFTD patients with psychiatric diagnoses. This is a key factor that may contribute to delay the diagnosis of a neurodegenerative disease (31). As mentioned before, our findings regarding a higher frequency of psychiatric misdiagnosis in women with bvFTD agree with those described in other well-characterized cohorts in the United States of America (15). However, it should be noted that unlike previous studies,

our study has been carried out in a European population with a public healthcare system and universal access. This is an important difference because in a public system the time from the onset of symptoms to the consultation, the access to the health system and the quality of care received are independent of the patient's socioeconomic level and may decrease healthcare access bias (32).

The MMSE is a useful tool to measure the cognitive impairment in bvFTD, as it has been shown in previous studies (20). The MMSE score was lower in female patients with bvFTD but not in the other presentations. We found higher impairment restricted to highly probable bvFTD subgroup. The time from the estimated symptom onset to diagnosis varied between syndromes. Concretely, we found a higher time to diagnosis in the bvFTD. This finding may suggest a delay in the diagnosis of the bvFTD. However, this difference was not significant when comparing women and men. We found that the MMSE impairment was not associated with more time to diagnosis in women. Although one might initially presume that MMSE impairment implies a longer time from onset to diagnosis, this hypothesis is contradicted by our data. However, it should be noted that the time from symptom onset to the diagnosis is an estimation that can be influenced by the caregivers' ability to identify the earliest changes in the patient's personality. Thus, this estimation can be influenced by several factors escaping out of our control. By the contrary, the MMSE is an objective score widely used by neurologists.

Not all the studies support the existence of sex-related differences in the bvFTD (24). This may be due to socio-cultural factors (many family members do not consider personality change as a disease), factors in the differential diagnosis (diagnosing FTD syndromes may be difficult for physicians and general neurologists), or factors from the patient's neurological study (the lack of use of biomarkers to support the diagnosis). Another possibility is that women may display more aggressive phenotypes of FTD. However, there is no evidence to support this hypothesis in the literature. Taken together, our results highlight the importance of identifying diagnosis biases of FTD. Further studies should specifically address the factors contributing to sex-related differences in the diagnosis of FTD among general neurologist and psychiatrists.

The main strength of this study is the deep phenotyping of the patients included. CSF biomarkers ruled out AD in the patients included in this study. Thus, we have low probability of AD misdiagnosis. Furthermore, in our cohort we considered the wide range of FTD-related syndromes. Finally, our study is the first to assess sex-related differences in the diagnosis of FTD in European population with a public healthcare system.

This study has also some limitations. Although we think that a cross-sectional design is the most feasible way to study sex-related differences in the clinical presentation of FTD, our cohort is made up of patients from a single center. Thus we cannot exclude the possibility of a selection bias (33). Further multicenter studies are needed to improve our understanding of potential sex-related differences in the diagnosis of FTD in our environment.

In conclusion, the bvFTD is more frequently diagnosed in men in our environment, and women are diagnosed at a more advanced stage with a higher frequency of previous psychiatric diagnosis. In sum, our results suggest that women diagnosed with the bvFTD may be more frequently misdiagnosed with psychiatric conditions in our environment. This work highlights the importance of sex-related biases for the diagnosis of the bvFTD and the need of educational activities to improve the knowledge about FTD among general practitioners and the population in our environment. Further multicenter studies are needed to confirm our observations and disentangle the underpinnings of sex-related biases in the diagnosis of the bvFTD.

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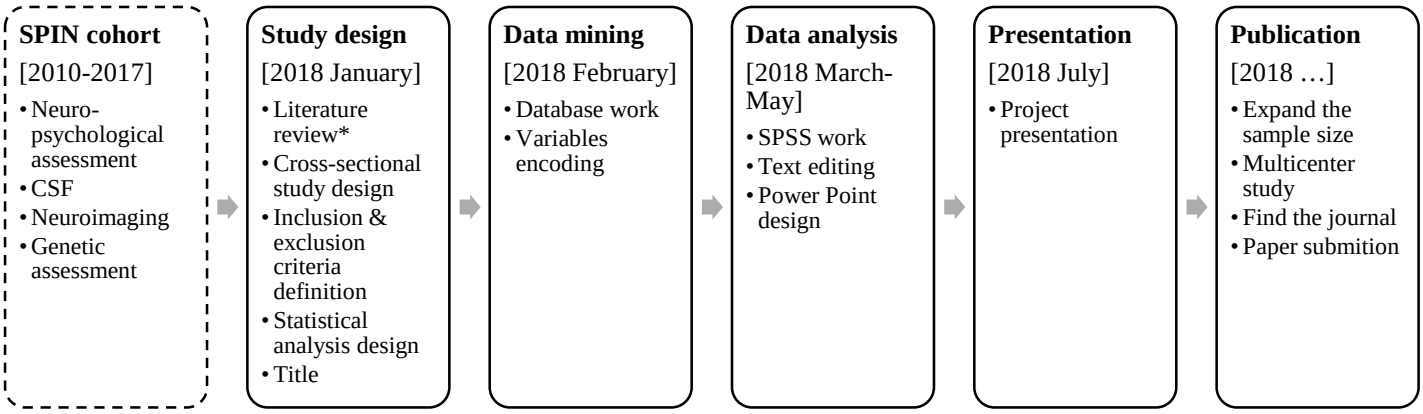
ANNEXES

ANNEX 1: Project timeline



***Literature review**:

- Pubmed search:

Search details	**Search results**
("Frontotemporal Dementia"[Mesh]) AND "Sex"[Mesh]	0
("Frontotemporal Dementia/diagnosis"[Mesh]) AND "Sex"[Mesh]	0
("frontotemporal dementia"[MeSH Terms] OR ("frontotemporal"[All Fields] AND "dementia"[All Fields]) OR "frontotemporal dementia"[All Fields]) AND ("sex"[MeSH Terms] OR "sex"[All Fields]) AND ((hasabstract[text] AND "loattrfull text"[sb]) AND "2008/01/18"[PDAT] : "2018/01/15"[PDAT] AND "humans"[MeSH Terms])	98

- Relevant papers

1. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. **Dialogues Clin Neurosci**. 2016;18(4):437–46

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ANNEX 2: MMSE (Mini-mental state examination) (34,35)

Paciente.....Edad.....
Ocupación.....Escolaridad.....
Examinado por.....Fecha.....

ORIENTACIÓN

- Dígame el día.....fecha……Mes.....Estación.....Año..... **___5**

- Dígame el hospital (o lugar) .....planta.....
  Ciudad…….....Provincia.....Nación…..... **___5**

FIJACIÓN

- Repita estas tres palabras; PELOTA, CABALLO, MANZANA (hasta que las aprenda) **___3**

CONCENTRACIÓN Y CÁLCULO

- Si tiene 30 monedas y me va dando de tres en tres ¿cuantas le van quedando? **___5**

- Repita estos tres números: 5,9,2 (hasta que los aprenda). Ahora hacia atrás **___3**

MEMORIA

- ¿Recuerda las tres palabras de antes? **___3**

LENGUAJE Y CONSTRUCCIÓN

- Mostrar un bolígrafo. ¿Qué es esto ?, repetirlo con un reloj **___2**

- Repita esta frase: EN UN TRIGAL HABÍA CINCO PERROS **___1**

- Una MANZANA y una PERA, son frutas ¿verdad?
  ¿qué son el ROJO y el VERDE? **___2**

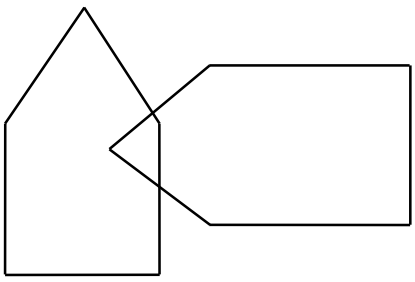
- ¿Que son un PERRO y un GATO? **___3**

- Coja este papel con la mano derecha dóblelo y póngalo encima de la mesa **___1**

- Lea esto y haga lo que dice: CIERRE LOS OJOS **___1**

- Escriba una frase **___1**

- Copie este dibujo **___1**



Puntuación: ___/35

ANNEX 3: Rascovsky criteria

Neurodegenerative disease

- Must be present for any FTD clinical syndrome
- Shows progressive deterioration of behavior and/or cognition by observation or history

Possible bvFTD

- Three of the features (A–F) must be present; symptoms should occur repeatedly:
  - A. Early (within first 3 years) behavioral disinhibition
  - B. Early (within first 3 years) apathy or inertia
  - C. Early (within first 3 years) loss of sympathy or empathy
  - D. Early (within first 3 years) perseverative, stereotyped or compulsive/ritualistic behavior
  - E. Hyperorality and dietary changes
  - F. Neuropsychological profile: executive dysfunction with relative sparing of memory and visuospatial functions

Probable bvFTD

- All the following criteria must be present to meet diagnosis
  - A. Meets criteria for possible bvFTD
  - B. Significant functional decline
  - C. Imaging results consistent with bvFTD (frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)

Definite bvFTD

- Criteria A and either B or C must be present to meet diagnosis:
  - A. Meets criteria for possible or probable bvFTD
  - B. Histopathological evidence of FTLD on biopsy at post mortem
  - C. Presence of a known pathogenic mutation

Exclusion criteria for bvFTD

- Criteria A and B for possible bvFTD must both be answered negatively; criterion C can be positive for possible bvFTD but must be negative for probable bvFTD:
  - A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
  - B. Behavioral disturbance is better accounted for by a psychiatric diagnosis
  - C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

ANNEX 4: Informed consent

A) CONSENTIMIENTO INFORMADO – PROYECTO COHORTE SPIN

TÍTULO DEL ESTUDIO:
Búsqueda de biomarcadores en el diagnóstico precoz de las demencias degenerativas primarias.

OBJETIVO:
Nos gustaría pedir su permiso para incluirle en este estudio de investigación. El motivo es que usted o alguien en su familia ha sido diagnosticado de pérdida de memoria, o demencia. El objetivo de este estudio es aprender más acerca de la evolución, similitudes y diferencias entre las distintas enfermedades degenerativas que producen pérdida de memoria u otros síntomas similares.
En este estudio esperamos conocer la utilidad de distintos parámetros en el diagnóstico de enfermedades que alteran la memoria u otras funciones intelectuales. No obstante, algunos de estos estudios no forman parte de la evaluación rutinaria de los pacientes con pérdida de memoria. Los resultados tienen interés exclusivamente desde el punto de vista de investigación y por este motivo no se le comunicarán los resultados de este estudio a menos que tengan relevancia clínica para usted.

PERSONAS DE CONTACTO:
Si tiene preguntas referentes a este estudio puede contactar con los distintos miembros de la Unidad de Memoria (Dr. Alberto Lleó, Dr. Juan Fortea, Dr. Daniel Alcolea, Dra. María Carmona, Dra. Estrella Morenas, Dra. Roser Ribosa o Dr. Rafael Blesa):

- Teléfono de estudios de la Unidad de Memoria del Servicio de Neurología del Hospital de Sant Pau: 618.846.138 (lunes a viernes de 9:00 a 17:00h)
- Correo electrónico Unidad de Memoria: estudismemoria@santpau.cat

PROCEDIMIENTOS:
Si acepta participar y usted ya se visita en la Unidad de Memoria, se revisará su historia clínica y algunos datos relevantes como edad, diagnóstico, historia familiar y pruebas complementarias. Si usted no se visita en la Unidad de Memoria se le realizará una evaluación de unos 45 minutos donde se le preguntarán aspectos relacionados con su salud y se le realizará una evaluación breve de su memoria y otras facultades intelectuales. Esta información es de gran utilidad para conectar los resultados de la investigación con los hallazgos médicos.
Durante un período de dos años se realizará un seguimiento clínico mediante visitas médicas semestrales en la Unidad de Memoria y, además de las pruebas que forman parte de la evaluación rutinaria de los pacientes con pérdida de memoria, se solicitará su colaboración para la realización de las siguientes exploraciones:

1. **Análisis de sangre:** Estas muestras se utilizarán para extraer *ADN* (el ADN es el material del que están constituidos los genes) y para analizar los niveles de *determinados parámetros* en la sangre. Se realizará un total de 5 extracciones a lo largo de los dos años. Los riesgos derivados de la extracción de sangre son mínimos, e incluyen dolor leve o un pequeño morado en la zona de la extracción. Los resultados de estos análisis tienen interés únicamente desde el punto de vista de investigación, por lo que los resultados no le serán comunicados. Estos análisis son independientes de la analítica rutinaria que se suele solicitar a todos los pacientes con problemas de memoria al inicio de su evaluación, y cuyos resultados, sí le serán comunicados.

2. **Resonancia Magnética cerebral (RM)**: La RM cerebral es una prueba de imagen que permite ver con detalle la estructura de su cerebro sin necesidad de utilizar radiaciones ionizantes en su adquisición. Frecuentemente esta prueba forma parte de la evaluación rutinaria de los pacientes

con problemas de memoria. En su caso, se realizará con una doble finalidad: asistencial y de investigación. Cualquier dato de relevancia clínica le será comunicado en la visita médica correspondiente. Se realizará una RM al inicio del estudio y posteriormente con una frecuencia anual (un total de 3). Las contraindicaciones para la realización de esta prueba incluyen: tener implantado un marcapasos, desfibrilador automático, clips aneurismáticos o cualquier prótesis metálica no extraíble.

3. **Punción lumbar** (una al inicio y otra al año de seguimiento): consentimiento independiente. Para preservar la confidencialidad de esta información, los datos pertenecientes a este estudio no se incluirán en la historia clínica convencional, sino en un fichero aparte en un lugar protegido. La información recogida, la muestra de sangre y la de líquido cefalorraquídeo serán asignadas a un código. La clave de este código será almacenada por el investigador principal en un archivo independiente. Los resultados de dichas exploraciones se introducirán en una base de datos independiente creada especialmente para este estudio. En esta base no se utilizará su nombre, ni ningún otro dato que pueda identificarle a usted, sino sólo el código asignado a este estudio. La información es totalmente confidencial y sólo será accesible a los miembros del equipo investigador.

Es posible que le solicitemos que contacte con algún miembro de su familia. En este caso, le daremos copias de esta carta para que se la entregue a sus familiares para que ellos se pongan en contacto con nosotros.
Este estudio es totalmente voluntario, puede retirarse cuando lo desee y tiene derecho a solicitar que toda la información referente a usted, así como la muestra de sangre sea destruida en cualquier momento. No existen beneficios directos para usted en este estudio, pero es posible que los resultados de este estudio permitan un mayor conocimiento de la evolución de las enfermedades degenerativas que ocasionan pérdida de memoria y que pueda contribuir al desarrollo de mejores tratamientos para curar o prevenir estas enfermedades. No es probable que la información derivada de este estudio tenga implicaciones directas para su salud. No obstante, si usted lo desea, puede solicitar los resultados de los estudios realizados con sus muestras.

COSTES:
El estudio no tiene coste económico para usted.

OPCIONES:
1. Nos da permiso para contactar con usted en el futuro para pedirle otra muestra de sangre?
SI__ NO__
2. Nos autorizaría a compartir la información con otro equipo investigador siempre que fuera anónima (toda la información que pueda identificarle sería eliminada)?
SI__ NO__

FIRMAS:

Paciente, familiar o representante legal (señalar)	Fecha
Médico (Nº colegiado)	Fecha

B) CONSENTIMIENTO INFORMADO – PUNCIÓN LUMBAR

El Sr./Sra. .....
(escribir el nombre y los dos apellidos)

con DNI nº ..... en calidad de .....
(en caso de minoría de edad o incapacidad, especificar parentesco, tutor o representante legal)

del paciente Sr(a) .....
(escribir el nombre y los dos apellidos)

DESCRIPCIÓN DEL PROCEDIMIENTO

La punción lumbar es un procedimiento mediante el cual, se introduce una aguja en el canal medular para extraer una muestra del líquido en el que está bañado el sistema nervioso central (cerebro y médula espinal), llamado líquido cefalorraquídeo.
Se realiza mediante la introducción de una aguja en la zona lumbar. Este es el lugar más seguro para realizar dicha prueba, ya que queda por debajo del extremo final de la médula espinal y no existe riesgo de dañarla. Su médico le indicará cuál es la posición adecuada que deberá adoptar para la realización de esta prueba. Frecuentemente se utiliza un anestésico local que reduce al mínimo las molestias de la punción.
Este es un procedimiento que se realiza prácticamente a diario en el servicio de Neurología.

POR QUÉ

En la práctica clínica habitual, este procedimiento se realiza con la finalidad de diagnosticar una infección o inflamación del sistema nervioso. En ocasiones también se utiliza para registrar la presión del líquido o para administrar medicación.
En su caso, pretendemos medir determinados parámetros bioquímicos que pueden estar en relación con la enfermedad que le ha sido diagnosticada. La determinación de estos parámetros ya está siendo de utilidad diagnóstica en otros países, y se realiza de manera prácticamente rutinaria en personas que tienen su misma enfermedad, aunque aquí, por el momento, sólo se realiza con objetivos de investigación.

RIESGOS DEL PROCEDIMIENTO

Las complicaciones o riesgos que pueden ocurrir como consecuencia de este procedimiento se detallan a continuación:
La complicación más común (2-5%) es el dolor de cabeza. Se debe a la disminución de presión secundaria a la extracción de líquido, y algunas maniobras habituales para disminuirlo son el reposo en cama e ingesta abundante de líquidos durante las horas siguientes a la punción. De todas formas, si apareciera, puede pedir a la enfermera un calmante.
Las infecciones (meningitis, espondilodiscitis, celulitis) son raras al realizarse en condiciones estériles.
Otras complicaciones poco frecuentes son hematomas locales en el sitio de la punción, apareciendo con mayor frecuencia en pacientes con enfermedades hematológicas o tratados con fármacos anticoagulantes. Excepcionalmente se han descrito hematomas intracraneales secundarios a la hipotensión del LCR, así como la herniación transtentorial, complicación potencialmente mortal y que puede aparecer en pacientes con algunos procesos intracraneales como grandes masas, procesos que por medio de la historia clínica y las pruebas complementarias habrán sido razonablemente descartados en su caso.

Expone que:
El Dr(a). ..... del Servicio de NEUROLOGIA me ha explicado en qué consiste una punción lumbar y cuál es el motivo por el que se me debería realizar. También me ha informado de las complicaciones generales de este procedimiento y me ha comunicado que mis riesgos personales son:
.....
.....

En caso de aparecer alguna de las complicaciones mencionadas, se tomarán por parte del Hospital todas las medidas necesarias para corregirla.

La información me ha sido dada de forma comprensible y mis preguntas han sido contestadas, por lo cual autorizo al equipo médico que me trata a realizar la exploración propuesta.

Conozco que, en cualquier momento y sin necesidad de ninguna explicación, puedo revocar el consentimiento que estoy dando.

FIRMAS:

Paciente, familiar o representante legal (señalar)	Fecha
Médico (Nº colegiado)	Fecha

Barcelona, _____de_____ del 20____.

C) CONSENTIMIENTO INFORMADO – COLECCIÓN DE MUESTRAS BIOLÓGICAS

El Sr./Sra. .....
(escribir el nombre y los dos apellidos)

con DNI nº ..... en calidad de .....
(en caso de minoría de edad o incapacidad, especificar parentesco, tutor o representante legal)

del paciente Sr(a) .....
(escribir el nombre y los dos apellidos)

CONFIRMA QUE:

1. Autoriza a que el material biológico obtenido de los procedimientos explicados en la hoja de información se guarde en una colección de muestras biológicas con fines de investigación biomédica.
SI__ NO__

2. Nos autorizaría a compartir la información y las muestras biológicas incluidas con otro equipo investigador siempre que fueran anónimas (toda la información que pueda identificarle sería eliminada)?
SI__ NO__

3. Autoriza a ser contactado en el caso de que se requiera más información o muestras biológicas adicionales.
SI__ NO__ Teléfono o e-mail de contacto:

4. Deseo que se me comunique la información derivada de la investigación que sea médicamente relevante y aplicable para mi salud o la de mi familia.
SI__ NO__

Teléfono o e-mail de contacto:

FIRMAS:

Paciente, familiar o representante legal (señalar)	Fecha
Médico (Nº colegiado)	Fecha

Barcelona, _____de_____ del 20____.