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ORIGINAL COMMUNICATION

Amnesia in frontotemporal dementia: shedding light on the Geneva historical data

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Abstract Recent accumulated evidence indicates that episodic memory impairments could be part of the initial clinical expression of frontotemporal dementia (FTD). An early study on this issue was carried out by Constantinidis and colleagues in 1974, but it was subsequently overlooked for a long period of time. The scope of the present research was: (a) to explore the presence of early episodic memory impairments in the entire population of neuropathologically confirmed FTD patients from the Geneva brain collection; and (b) to expand the present insight on the association between the initial symptomatology and various characteristics, namely gender, age at onset, disease duration, and presence of Pick body neuropathology. A careful review of the records of 50 FTD patients hospitalized at the Department of Psychiatry of the Bel-Air Hospital, Geneva, Switzerland, from 1929 to 1999, was conducted. Further in-depth neuropathological analysis with novel immunohistological methods was carried out in 37 of the cases. The data showed that memory impairments were the first clinical symptom in several of the patients. In addition, this specific phenotypic expression of FTD was associated with the female gender, advanced age, and positive Pick body neuropathology. The current findings give the opportunity to historically vindicate the early work of Constantinidis and colleagues. In addition, the novel observations about the association of episodic memory impairments with the female gender and positive Pick body neuropathology add to the existing knowledge about this phenotypic expression of FTD.

Keywords Frontotemporal dementia · Episodic memory · Brain collection · Neuropathology

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Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder that in ages below 65 years has prevalence similar to that of Alzheimer's disease (AD) [30]. FTD is an umbrella term that covers three different types of clinical syndromes: (a) the behavioral variant of FTD (bv-FTD) that is classically characterized by radical personality and behavioral changes; (b) the semantic dementia, the most important feature of which is the progressive loss of knowledge about words and objects; and (c) the progressive non-fluent aphasia that is characterized by effortful production of language, grammar errors and motor speech deficits [30]. In reference to the underlying neuropathology, 40 % of the patients show abnormal aggregation of the microtubule binding protein tau, 50 % show the 43 kDa TAR DNA-binding protein (TDP-43) inclusions, and 10 % show the fused in sarcoma RNA-binding protein (FUS) inclusions [21, 22]. At present, the term "Pick disease" refers to a subtype of the broader tau

molecular class containing 3R tau that is characterized by spherical argyrophilic neuronal inclusions (Pick bodies) and ballooned neurons (Pick cells) [29]. The clinical syndrome was described by Arnold Pick in 1892 [14], and originally the term "Pick disease" covered all cases called today FTD.

The diagnostic criteria of the various clinical types of FTD that were widely used during the last decades were designed with the purpose of increasing the specificity of the diagnosis by excluding cases that followed a pattern of symptomatology commonly observed in AD and in vascular dementia (VaD) [27]. Thus, the presence of severe amnesia early in the course of the disease was considered as an exclusion feature that precluded the diagnosis of any of the clinical syndromes of FTD [27], thereby leading to specificity levels that ranged from 90 to 100 % [23, 28]. However, the level of sensitivity achieved by the specific set of criteria was only around 50 % [31].

Notably, evidence provided by recent research indicates that early episodic memory disturbance should not exclude the diagnosis of FTD [11]. In 2001 the case of a patient with pathologically verified FTD who had severe amnesia from the earliest stages of the disease was reported [7]. Subsequent studies that used large sample sizes detected also FTD patients with marked episodic memory deficits at the disease onset [11, 13]. Remarkably, in a small percentage of patients, memory loss was the only symptom at the beginning of the disease [11]. In agreement with this finding, previous research has shown that according to the view of the caregivers, memory impairments are more commonly observed than language disturbance and behavioral changes as the first symptom of the disease [3]. Moreover, comparison of the episodic memory performance between patients with bv-FTD and patients with AD revealed a similar degree of impairment in the two groups, thus indicating that the presence of episodic memory attenuation does not exclude the possibility of an underlying FTD pathology [15]. Rascovsky et al. [31] by reviewing the clinical records of a large sample of patients with pathologically verified FTD developed a revised set of criteria for the diagnosis of this disorder that do not consider early severe amnesia as a feature that excludes FTD anymore. According to the aforementioned research group, elimination of certain exclusion criteria, such as early amnestic and spatial disorientation symptoms, improves the sensitivity of the diagnosis of FTD, since 15 out of 137 patients with pathologically verified bv-FTD had developed a severe amnestic picture during the initial stages of the disease [31]. In the same vein, Hornberger and Piguet [14] by reviewing a wide range of findings argue that especially in the case of bv-FTD episodic memory deficits may appear early in the course of the disease in a similar way to that of AD, thus complicating the diagnostic process.

The aforementioned studies that show the presence of early episodic memory impairments in some cases of FTD were carried out after the development of the diagnostic criteria by Neary et al. [27] that considered the presence of early severe amnesia as an exclusion feature. Nonetheless, long before the work of Neary et al. [27], Constantinidis and colleagues reported that 18 out of a total of 32 patients with pathological verification of FTD had episodic memory impairments during the initial stages, similar to those observed in AD [8]. Possibly, this important observation was overlooked because the diagnostic criteria proposed by Neary et al. [27] were developed in a period of time when there was a strong drive to improve the specificity of the diagnosis of FTD and clearly differentiate this specific type of dementia from that of AD, which had the prominent role in dementia research.

The objective of this study was to look for the presence of early episodic memory impairments in the entire patient population with a pathological diagnosis of FTD from the Geneva brain collection [18] as well as to investigate the association between the initial pattern of symptoms and various characteristics, such as gender, age at onset, disease duration and presence of Pick body neuropathology. In addition, an additional goal was to explore the association between the clinical expression of the disease and the findings of a detailed neuropathological evaluation that utilized novel immunohistological methods.

Methods

Patients: FTD diagnosis

A careful review of the full clinical records of patients hospitalized at the Department of Psychiatry of the Bel-Air Hospital, Geneva, Switzerland, from 1929 to 1999, diagnosed as having FTD was carried out. Subjects were admitted in the study provided that their files included pathological verification of the disease as well as full data about the initial clinical symptoms and the course of the disease. In addition to the collection of detailed clinical information, the initial evaluation included the application of sufficient and adequate neuropsychological clinical testing that permitted the detection of the type of amnestic deficits (e.g., episodic vs. semantic) as well as of any language or executive impairments. Based on this information, a subject was placed in the "memory disorder" group only if sufficient data were available to document a clear episodic memory impairment that was described often in the clinical files as "deficits de la memoire de fixation". Regarding the presence of language deficits, a general "language disorder" category was used for the classification because the data were not clear enough for

placing the patients either in the subtype of semantic dementia or of progressive non-fluent aphasia. However, even with modern neuropsychological language testing it has been shown that some patients cannot be clearly classified into one of the language-related variants of FTD (semantic, non-fluent, logopenic) [12]. We also noted that as the time period of data collection covers 70 years, various tests have been used. Some of them were used in the clinic by "behavioral neurologists" of that time (e.g., Professors: J. Ajuriaguerra, J. Richard, R. Tissot) and do not belong to the class of the widely known formal neuropsychological tests.

From an initial pool of 59 cases, nine were excluded because of the presence of alcohol dependence or because of missing data. Hence, a total of 50 patients, with neuropathological diagnosis of FTD and full description of the clinical symptomatology were included in the study. Further in-depth neuropathological analysis was carried out in 37 cases, because in 13 cases insufficient tissues were available. According to the pattern of symptoms that were present during the first year of the disorder, patients were classified into five categories: (a) memory disorder only (M), (b) language disorder only (L), (c) behavioral disorder only (B), (d) behavioral and memory disorder (B + M), and (e) behavioral and language disorder (B + L). The initial diagnosis and the clinical diagnosis at death according to the pattern of the first symptoms are presented in Tables 1 and 2, respectively. In addition, Table 3 lists the frequency of the various categories of the initial symptomatology for the following chronological periods: (a) 1929–1955, (b) 1956–1979, and (c) 1980–1999. The frequency of patients with an early amnestic picture remained generally similar across the three chronological periods.

Table 1 Initial clinical diagnosis according to the pattern of the first symptoms

Initial diagnosis							
First symptom	*N*	AD	VaD	PiD	AD/VaD	AD/PiD	NS-D
Only memory disorder	23	13	3	–	2	1	4
Only language disorder	10	–	1	1	–	–	8
Only behavior disorder	11	–	–	1	–	–	10
Memory and behavior disorder	5	–	–	1	–	1	3
Language and behavior disorder	1	–	–	–	–	–	1

N number of cases, *AD* Alzheimer's disease, *VaD* vascular dementia, *PiD* Pick's disease, *NS-D* non-specified dementia

Table 2 Clinical diagnosis at death according to the pattern of the first clinical symptoms

Diagnosis at death							
First symptom	*N*	AD	VaD	PiD	AD/VaD	AD/PiD	NS-D
Only memory disorder	23	4	3	6	2	2	6
Only language disorder	10	–	1	3	1	–	5
Only behavior disorder	11	3	–	5	–	–	3
Memory and behavior disorder	5	–	–	1	–	1	3
Language and behavior disorder	1	–	–	–	–	–	1

N number of cases, *AD* Alzheimer's disease, *VaD* vascular dementia, *PiD* Pick's disease, *NS-D* non-specified dementia

Table 3 Number of patients in various chronological periods according to the pattern of the initial symptomatology

First symptom	No. of cases according to chronological period		
	1929–1955	1956–1979	1980–1999
Only memory disorder	6	7	10
Only language disorder	2	3	5
Only behavior disorder	4	4	3
Memory and behavior disorder	0	4	1
Language and behavior disorder	0	1	0
Total	12	19	19

In-depth neuropathological analysis

Brain tissues were available in 37 from the initial 50 autopsy cases. In this final neuropathological sample of 37 cases, 27 were previously diagnosed as tau-negative FTD and 10 as FTD with tau-positive Pick bodies (PiD). The mean age at death was 72.0 ± 9.0 years (range 56–90 years), nine men (67.0 ± 5.8 years) and 28 women (73.6 ± 9.4 years).

From the left hemisphere of the formalin-fixed brains, tissue blocks were taken from the hippocampus, including the dentate gyrus (DG), as well as the inferior temporal cortex (TC—Brodmann area 20), and the frontal cortex (FC—Brodmann area 9). Tissue blocs were embedded in paraffin and cut into 14-µm-thick sections. Serial sections were stained with hematoxylin–eosin, cresyl-violet, and with antibodies against tau protein (AT8 monoclonal, 1/1000, Thermo Scientific, Rockford, IL, USA), ubiquitin (polyclonal, 1/50, Sigma–Aldrich, Saint Louis, MO, USA), TDP-43 (polyclonal, 1/50, Sigma–Aldrich, Saint Louis, MO, USA), FUS (polyclonal, 1/100, Sigma–Aldrich, Saint Louis, MO, USA), β-amyloid (4G8 monoclonal, 1/1000, Signet Laboratories, Dedham, Mass, USA) and α-synuclein (polyclonal, 1/1000, Sigma–Aldrich, Saint Louis, MO, USA).

Neuronal densities and densities of tau, ubiquitin and TDP-43 positive inclusions were counted in the dentate gyrus, the superficial temporal, and the frontal neocortex using a computer-assisted morphometry system consisting of a Zeiss Axioplan, two photomicroscopes equipped with a LEP (Ludl Electronic Products, Hawthorne, NY, USA) computer-controlled motorized stage, a color digital video camera, a QM personal computer, the StereoInvestigator morphometry and stereology software (MicroBrightField, Wiliston, VT). In addition, the Braak stages for neurofibrillary tangles [5] and Thal phases [34] for amyloid deposition were defined.

Statistical analysis of the total sample of patients with FTD

Differences in the frequency of the various patterns of symptomatology that were present during the first year of the clinical course of the disorder were investigated with the application of the Chi-square test for goodness of fit. In addition, the same test was used to explore differences in the frequency of the various types of the initial symptomatology in patients with and without Pick body neuropathology. The presence or not of an association between gender and type of the first clinical symptoms, namely memory impairments, language impairments, and behavioral impairments, was investigated with the use of the Chi-square test for independence. In addition, the same type of analysis was applied to study the association between the neuropathological classification of the disease (Pick vs. non-Pick) and type of the initial clinical symptoms. The Fisher's exact probability test was applied for the estimation of statistical significance when the lowest expected frequency in any cell was below 5.

To assess the presence or absence of significant differences in the age at onset and duration of the disease between patients with positive and negative Pick body pathology, an independent-samples *t* test analysis was applied. The same type of analysis was also used for the investigation of differences in the age at onset and duration of the disease depending on the kind of the first clinical symptoms. Significance was set at 0.05. The Statistical Package for the Social Sciences (SPSS), version 17 (Chicago, IL) was used to analyse the data.

Statistical analysis of the 37 cases with in-depth neuropathological evaluation

Statistical analyses were carried out using the Stata, version 12.1 (Stata Corporation, College Station, TX, USA).

Comparisons between cases with memory impairment as the first sign of the disease versus other symptoms were assessed by applying the Fisher exact test for categorical variables and the Mann–Whitney U test for continuous variables, such as neuron- and inclusion densities (tau, ubiquitin, TDP-43), for each of the three studied areas. Continuous variables were successfully normalized when using a square root transformation. Simple logistic regression was applied to predict binary outcome from each continuous variable in each area.

Multiple logistic regression analyses were applied to predict binary outcome (cases with memory impairment as the first sign of the disease versus other type of initial symptoms) in a first set of models using neuron- and inclusion densities in each of the three studied areas (DG, TC and FC) and in a second set of models using results of all three areas (DG, TC and FC) for each of the neuropathological parameters (neuron densities, general inclusion densities, tau-inclusion and TDP-43 density). Comparisons among the three clinical groups (language, behavior, or memory impairment as first sign of disease) were performed using one-way ANOVA and the Kruskal–Wallis non-parametric ANOVA.

Results

Total sample of patients with FTD

Fifty patients with FTD, 36 females and 14 males, were included in the initial phase of the analysis. The mean age at

Table 4 Mean (SD) age at onset and duration of the disease in patients with frontotemporal dementia according to gender, pattern of the first clinical symptoms, and neuropathological classification of the disease

Patient's characteristics	*N*	Age at onset (years)	Duration (years)
Total	50	64.3 (10.3)	7.9 (4.3)
Male	14	57.9 (9.6)	8.0 (3.9)
Female	36	66.8 (9.5)	7.9 (4.5)
Only memory disorder	23	67.1 (11.0)	7.9 (4.8)
Only language disorder	10	64.8 (8.1)	7.4 (3.5)
Only behavior disorder	11	58.0 (10.3)	9.9 (4.2)
Memory and behavior disorder	5	64.0 (7.4)	4.8 (2.2)
Language and behavior disorder	1	66.0	7.0
FTD-tau (PiD)	15	65.0 (10.3)	9.0 (4.7)
FTD non-tau	35	64.0 (10.4)	7.5 (4.1)

onset of the disease was 64.3 years (SD 10.3, range 37–85). In groups M, B and L were classified 23 (46 %), 11 (22 %) and 10 (20 %) patients, respectively (Table 4). Application of the Chi-square test for goodness of fit showed that the number of patients placed in group M was significantly greater than those placed in group B [$\chi^2(1, n = 34) = 4.24$, $p = 0.040$], and group L [$\chi^2(1, n = 33) = 5.12, p = 0.024$]. On the other hand, a similar number of individuals was placed in group B and group L, [$\chi^2(1, n = 21) = 0.05$, $p = 0.827$].

A significant association between gender and memory impairments as the first clinical symptom was observed that reflected the greater frequency of early memory deficits in the female subgroup, $\chi^2(1, n = 50) = 4.73$, $p = 0.030$, phi = 0.31. Specifically, 20 (55.6 %) out of 36 female patients had memory impairments as the first clinical symptom, whereas only 3 (21.4 %) out of 14 male patients developed memory deficits at the onset of the disease. Investigation of the association between gender and language impairments as the first clinical symptom of the disease revealed a statistically significant opposite pattern, Fisher exact test $p = 0.020$. Specifically, 6 (42.9 %) out of 14 male patients had language impairments as the first clinical symptom, whereas only 4 (11.1 %) out of 36 female patients followed the same clinical course. No significant association between gender and behavioral impairments was found, $\chi^2(1, n = 50) = 0.49$, $p = 0.476$.

The initial neuropathological examination detected Pick bodies in 15 (30 %) of the patients; 9 (60 %) of them were classified in group M, 2 (13 %) in group L, 2 (13 %) in group B, and 2 (13 %) in group $B + M$ (Table 5). Comparison of the frequencies of groups M, L, and B in patients with positive Pick body neuropathology showed a significantly greater frequency of group M, $\chi^2(1, n = 13) = 7.54$, $p = 0.023$. Thirty-five patients (70 %) did not have Pick body neuropathology; 14 (40 %) of them were classified in group M, 9 (26 %) in group B, 8 (23 %) in group L, 3 (9 %) in group B + M, and 1 (3 %) in group B + L (Table 5). Conversely, comparison of the frequencies of groups M, L, and B in patients without Pick body neuropathology did not reveal significant differences in the frequencies of the three groups, $\chi^2(1, n = 31) = 2.00$, $p = 0.368$. The association between memory disorder as the initial symptom (yes/no) and neuropathological classification of the disease (Pick/non-Pick) did not reach the level of statistical significance, $\chi^2(1, n = 50) = 1.69$, $p = 0.193$, phi = 0.18. In addition, no significant relationship of the neuropathology of the disease was observed with the two other main patterns of clinical symptomatology, namely early language disorder [$\chi^2(1, n = 50) = 0.60, p = 0.702$, phi = 0.11] and early behavior disorder [$\chi^2(1, n = 50) = 0.94, p = 0.468$, phi = 0.14].

The mean age at onset of the disease was similar in the groups of patients with positive and negative Pick body neuropathology, $t(48) = 0.30$, $p = 0.762$. Exploration of age at onset differences depending on the pattern of clinical symptomatology showed a significantly younger age at onset in the group of patients that developed behavioral impairments as the first clinical symptom (mean = 58.0,

Table 5 Positive or negative Pick body neuropathology according to the pattern of the first clinical symptoms

First symptoms	Pick body neuropathology	
	Positive ($n = 15$)	Negative ($n = 35$)
Only memory disorder ($n = 23$)	9	14
Only language disorder ($n = 10$)	2	8
Only behavior disorder ($n = 11$)	2	9
Memory and behavior disorder ($n = 5$)	2	3
Language and behavior disorder ($n = 1$)	–	1

SD = 10.3) than in patients without behavioral impairments in the early stages of the disease (mean = 66.1, SD = 9.6), $t(48) = 2.43$, $p = 0.019$. In cases with memory impairments as the first clinical symptom there was a trend for an older age at onset than in cases without memory impairments (mean = 67.1, SD = 11.0 vs. mean = 61.9, SD = 9.1, respectively) that, however, failed to reach the level of statistical significance, $t(48) = 1.83$, $p = 0.073$. When the age at onset was compared between the groups of patients that developed memory impairments and behavioral impairments as the first clinical symptom, a significantly greater age at onset was observed in the amnestic group, $t(32) = 2.31$, $p = 0.027$. Finally, the presence or not of language impairments as the first clinical symptom was not associated with the age at onset of the disease (mean = 64.8, SD = 8.1 vs. mean = 64.2, SD = 10.8, respectively), $t(48) = 0.16$, $p = 0.870$. In reference to the duration of the disease, the analysis did not reveal significant differences between any of the pairs of the three main patterns of clinical symptomatology: (a) memory vs. behavior disorder, $t(32) = 1.17$, $p = 0.249$; (b) memory vs. language disorder, $t(31) = 0.30$, $p = 0.765$; (c) behavior vs. language disorder, $t(19) = 1.48$, $p = 0.155$. In addition, no significant differences in the duration of the disease were observed between cases with positive and negative Pick body pathology, $t(48) = 1.16$, $p = 0.251$.

Cases with in-depth neuropathological evaluation

In the series of 37 cases where novel immunohistological examination was performed, the mean age at death was not significantly different between groups with different types of inclusions: (a) FTLD-tau, PiD: 10 cases, mean age 73.6 ± 8.1 years, 2 male and 8 female; (b) FTLD-TDP: 17 cases, mean age 71.7 ± 9.7 years, 7 male and 10 female; (c) FTLD-ni (without tau, TDP-43, or ubiquitin inclusions): 8 cases, mean age 70.7 ± 9.5 years, all female; (d) FTLD-UPS (ubiquitin positive inclusions): 2 cases, 57 and 64 years, both female. None of the cases had FUS immunoreactive inclusions (FTLD-FUS).

There was no correlation between the first clinical sign and the neuronal densities in any of the regions studied. In addition, there was no correlation between the first clinical sign and the type of inclusions in any of the three studied areas. The most frequent neuropathological subtype was the FTLD-TDP (17 cases, 45.9 %), followed by FTLD-tau, PiD (10 cases, 27.0 %). Two cases showed ubiquitin inclusions only (FTLD-UPS) and in eight cases no inclusions of any type could be observed (FTLD-ni).

Seven out of the 37 cases showed mild tau pathology of AD type (one FTLD-tau, PiD; four FTLD-TDP; and two FTLD-ni), with a maximum Braak stage of two. Five of these cases had an amyloid deposition (one FTLD-tau, PiD; three FTLD-TDP; and one FTLD-ni) that manifested the following Thal phase range: Thal phase 3 ($n = 1$), Thal phase 2 ($n = 2$), and Thal phase 1 ($n = 2$). No α-synuclein reactive inclusions were observed. Vascular pathology was observed in five cases: two FTLD-tau, PiD cases with basal ganglia and occipital ischemic brain infarcts, and three other cases (two FTLD-TDP and one FTLD-ni) with cortical microinfarcts.

Discussion

The present study of the Geneva brain series showed that episodic memory impairments were present from the initial stages of FTD in a large number of the patients analyzed. Notably, when this pattern of symptomatology was present, the initial diagnosis that was usually made was AD or VaD. This observation is in agreement with recent research that indicates that episodic memory deficits may appear early in the course of the disease in a similar way to that of AD [11, 13, 14, 31]. This reverses the earlier prevailing view that amnesia appearing early in the course of the disease excludes the diagnosis of FTD [27]. In addition, this study provides the opportunity to historically vindicate the work of Constantinidis and co-workers who 40 years ago reported in patients with pathological verification of FTD the presence of episodic memory impairments during the initial stages of the disease, similar to those observed in AD [8]. Hence, the aforementioned research findings that were reported several decades earlier can be viewed as an early publication of the recent advances in the field of FTD, which was overlooked for a long period of time.

In reference to the presence of early amnesia in some cases of FTD, our study investigated factors that could be associated with the clinical course of the disease. Notably, episodic memory impairments as the initial symptom of FTD were more commonly observed in female that in male patients. To our knowledge, this is the first report that detects this gender-related pattern that puts women with FTD at a greater risk for early memory deficits and, therefore, it warrants further investigation. If not a type-I error, this finding could reflect gender differences in the susceptibility of various brain regions to FTD pathology, since the distribution of pathology appears to play a critical role on the pattern of clinical symptomatology [4, 7, 19]. In addition, the aforementioned observation could be related to previous research that indicates that the E4 allele of the apolipoprotein E gene increases the risk for frontotemporal dementia [9, 17] as well as that the E4 genotype has a greater impact on hippocampal pathology and memory disturbance in females than in males [2, 10]. On the other hand, the observation that language disturbance as the initial symptom is more common in the male than the

female patients could be considered to be in agreement with previous research indicating that language variants of FTD, such as semantic dementia, are diagnosed more frequently in the male population [6, 16].

The presence of a higher frequency of cases with initial episodic memory impairments than language or behavioral disturbances only in the subset of patients with Pick body inclusions supports the existence of a link between early amnesia and this specific type of neuropathology. This association has not been previously reported, but it should be mentioned that in the study of Graham et al. [11] the presence of Pick bodies in FTD patients that were amnesic from presentation was a quite common finding. In addition, three out of the five original cases reported by Arnold Pick between 1892 and 1904 which were subsequently shown to have Pick body neuropathology had evident signs of episodic memory impairment [14]. In addition to the predominance of early memory deficits in female patients and the link with positive Pick body pathology, another characteristic of the patients with an early amnestic syndrome was the greater age at onset than that observed in patients who initially developed behavioral disturbances. This observation is in agreement with previous research [1, 31] and could reflect an increased vulnerability of memory-related brain regions in older patients due to an interaction of the pathophysiology of FTD with aging processes that especially affect the functioning of episodic memory [20, 24].

The analysis showed similar duration of disease among the three groups of patients with the main patterns of clinical symptomatology. The value of this finding is that it drastically reduces the probability that the episodic memory impairments were preceded by overlooked behavioral or language disturbances. In addition, the case of missed prior language or behavioral symptoms does not fit with the observation that the duration of the disease in the early amnestic group was almost 8 years, a survival-span that is equivalent or even exceeds the prognosis in the vast majority of FTD cases [6, 26].

A limitation of the present research is its retrospective nature. Hence, the high frequency of cases with an early amnestic picture in the particular sample of FTD patients should not be considered as an indication that this phenotype is the most common form of the disease. A potential explanation of this finding could be that patients presenting an early amnestic syndrome were more readily diagnosed and admitted to the hospital than patients with the behavioral or language phenotypes. It is likely that some cases with a prominent behavioral phenotypic expression might not have been included in the specific cohort because they were considered at that time as pure psychiatric patients. Nonetheless, the identification of patients with neuropathologically verified FTD that develop episodic memory impairments in the initial stages of the disease similar to those observed in AD indicates that this pattern of symptomatology can also be part of the clinical spectrum of FTD. This observation is further supported by research findings that indicate the presence of hippocampal atrophy even during the early stages of FTD [6, 25, 32]. In addition, it should be noted that the limited number of patients in the different inclusion-types does not permit definite conclusions about the role of each pathological protein on the clinical expression of the disease. Finally, the absence of any FTLD-FUS cases in this cohort, which is a slightly disproportionate observation, could be explained by the relative underrepresentation in the current study of patients with bv-FTD. Previous research has reported that the FTLD-FUS neuropathology is most frequently observed in FTD patients that develop the behavioral variant of the disorder [33].

In conclusion, the present study sheds light on the original research about the presence of early episodic memory impairments in patients with FTD that was reported over 40 years ago and is in agreement with recent advances in the field of FTD. In addition, associations of the specific phenotypic expression of the disease with various parameters were detected, such as the female gender, advanced age, and presence of positive Pick body neuropathology. Since 1892, when Arnold Pick described for the first time the specific type of dementia, substantial progress has been made in the field of FTD. Nonetheless, the latest developments in the areas of neurobiology, neurogenetics, and brain imaging provide the capability to further expand our insight in the genetic, phenotypic and pathological heterogeneity of FTD.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards The Ethical Committee of the University Hospitals of Geneva has approved this retrospective autopsy study.

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