Onset Age and Clinical Heterogeneity of Dementias: A Diagnostic and Therapeutic Approach

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Abstract: Frontotemporal dementia (FTD) is the main differential diagnosis with early stages of Alzheimer's disease (AD). Usually, differential diagnosis between a first depressive episode and the beginning of an early degenerative dementia with mood disorders, either AD or FTD, can be difficult.

Objective: To evaluate the clinical characteristics of patients with senile and presenile onset dementia, to compare their neuropsychiatric and neuropsychological profiles according to onset age and to provide clinical approach.

Methods: A two year prospective-retrospective study was conducted. All patients were evaluated with a complete neuropsychiatric and neuropsychological battery, laboratory tests and neuroimaging. Healthy control subjects were also studied.

Results: Included 366 subjects were divided into over or under 65 years old, and then matched for educational level. AD was the most common cause of dementia in subjects over 65 years of age, followed by depression and FTD. Subjects younger than 65 years old, showed higher prevalence of depression followed by FTD, AD, and finally primary progressive aphasia (PPA). At younger ages, the highest severity of cognitive impairment, behavioral disorder and major depression were observed.

Conclusion: Onset age of cognitive and/or behavioral impairment may be one of the variables influencing the clinical heterogeneity of dementias. Many of the young-onset dementias may be potentially reversible so, its early identification and pathophysiology understand, increase pharmacological intervention opportunities of halting the cascade of events that lead inexorably to dementia. In the new era of biomarkers, their help in identifying each clinical phenotype could encourage their best use in clinical practice and help selecting more accurate pharmacological treatment.

Keywords: Alzheimer, depression, frontotemporal dementia, onset age, primary aphasia.

INTRODUCTION

The substantial increase of over 65 years old population due to better health care and life conditions, led to the exponential growth of age-related dementias such as, in particular, Alzheimer's disease (AD). The prevalence of this condition coupled with the economic, social and family costs causes a large concern to world public health [1-3].

Diagnosis of dementia is devastating at any age but, for young patients, it represents a particular impact. AD is the most common cause of dementia in later life. However, it can occur early in the fifth or sixth decade. The age of onset of AD has been associated with its clinical heterogeneity [4].

Frontotemporal dementia (FTD) is usually more common in younger than in older adults; however, AD is still the most prevalent early-onset dementia entity. FTD, characterized by early behavioral changes that can range from depression, apathy and disinhibition of behavior, poses the main differential diagnosis with early stages of AD. Usually, differential diagnosis between a first depressive episode and the beginning of an early degenerative dementia with mood disorders, either AD or FTD, is difficult [5-8].

Many of the young-onset dementias may be potentially reversible. Identification of genes responsible for the majority of dementias has led to understanding of their molecular pathology. In sporadic and late-onset cases the pathogenesis is still not so clear. Early identification of dementia and its pathophysiology understanding offers nowadays the possibility of future treatments specifically designed to halt the event cascade that inexorably leads to clinical manifestation of dementing illnesses [9].

The objectives of this study are to evaluate the clinical characteristics of patients with senile dementia onset (> 65 years) and presenile onset (<65 years) and to compare their neuropsychiatric and neuropsychological profiles according to onset age. Some diagnostic and therapeutic guidelines are given since early identification and management of neuropsychiatric symptoms (NPS) can help revert or delay

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the clinical manifestations that lead to high caregiver burden, poor prognosis, and higher rates of institutionalization and drug therapy; all of which contribute to an increased social and economic impact in people with dementia [5, 10].

MATERIALS AND METHODS

A two year prospective-retrospective study was conducted. All out-patients concurring spontaneously or referred by other professionals to a Research Laboratory of Memory were evaluated with a complete neuropsychiatric examination, a neuropsychological test battery, laboratory tests and neuroimaging scans. Patients' relatives were also evaluated as control subjects.

Included subjects were divided into two groups: under (>) or over (<) 65 years old, and then matched for educational level. Student t test was calculated to establish differences between groups due to years of school education and subject age belonging to the younger (65 or younger) or the older (66 or older) group.

Subjects in each group were divided according to their diagnosis or as normal control group. Subsequently, the following comparisons were established:

< 65 years *vs* > 65 years

< 65-normal *vs* > 65-normal

< 65-FTD *vs* > 65-FTD

< 65-AD *vs* > 65-AD

< 65-Depressive *vs* > 65-Depressive

Chi-square test was calculated to verify whether there was an association between subject age group and diagnosis.

Different types of diseases as well as their cognitive and behavioral profiles between younger and elder groups were compared; e.g. AD-young *vs* AD-elder.

t Student test was calculated to verify whether there were statistically significant differences between subject age group and their cognitive and behavioral profiles.

Homoscedasticity was checked through a Levene Test. A Mann-Whitney U test was used in small subgroup samples (n>30) where normality assumptions were not met. This test was also used when no homoscedasticity not normality assumptions were met. When the assumption of homoscedasticity was not met, the unequal variance values were reported. Comparisons were performed separately according to each diagnosis.

RESULTS

366 subjects, divided into > or < 65 years old and matched for educational level, showed no statistically significant differences according to age group (*p value* > 0.05).

Study groups included 158 subjects under 65 years and 208 over 65 years old.

Most frequent causes of dementia are summarized in Table **1**.

Statistically significant association ($\chi^2 = 85.424$, *p-value* = .000) was found in these cases:

1. There were fewer AD (RT = -5.1), and more normal (RT = 3.6) and depressive (RR = 2.8) subjects in the younger group (<65 years).
2. The opposite situation was observed in the older group (> 65 years). There were more subjects with AD (RT = 4.5), and less normal (RT = -3.2) and depressive subjects (RT = -2.5).

Table 1. Distribution of common causes of dementia by age group.

Age		Frequency (n)	Percentage (%)
Under 65	FTD	21	13,3
	AD	12	7,6
	Normal	61	38,6
	Depression	58	36,7
	PPA	6	3,8
	Total	158	100,0
Over 65	FTD	35	16,8
	AD	98	47,1
	Normal	28	13,5
	Depression	35	16,8
	PPA	12	5,8
	Total	208	100,0

Early Onset Dementia Features in Younger Subjects

In Table **2**, the median values and standard deviations calculated for each dementia cause in the younger group are summarized.

Late Onset Dementia Features in Elder Subjects

In Table **3**, the median values and standard deviations calculated for each dementia cause in the elder group are summarized.

Comparative Analysis

Different types of diseases as well as their cognitive and behavioral profiles between younger and elder groups were compared; e.g. AD-young *vs* AD-elder (Tables **4-8**).

FTD subjects showed age differences in Verbal IQ, Full test IQ, and presence of delusions. Elder subjects (66 years or more) had higher records in all tests. See Table **4**.

AD patients: statistically significant differences were found between age groups in Performance IQ, Full test IQ, and Euphoria/Negation symptoms presence. Performance IQ and Full test IQ scored higher in the elder group while Euphoria/Negation symptoms scored higher in the younger group. See Table **5**.

Normal subjects: statistically significant differences were found between age groups in MMSE, Serial recall, and the Beck inventory scores. In all cases, younger subjects showed higher scores. See Table **6**.

Table 2. Median values and standard deviations calculated for each dementia cause in the younger group.

	FTD		AD		Normal		Depression		PPA	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	58,52	5,13	60,00	4,32	55,28	9,50	53,84	9,64	62,50	3,01
Level of education (years)	10,76	3,59	6,42	2,35	12,08	4,23	9,52	4,27	12,17	4,79
Mini Mental State	26,10	3,78	20,50	5,26	29,05	1,58	28,26	1,84	24,00	9,33
Global CDR	0,90	0,20	0,90	0,21	0,36	0,22	0,45	0,17	0,58	0,20
Direct Span	5,10	1,61	4,82	1,40	5,92	1,40	5,16	1,37	4,00	1,26
Indirect Span	2,85	1,13	2,64	0,50	4,27	1,09	3,66	1,06	3,00	1,67
Clock test	5,10	2,49	4,00	2,28	6,61	0,98	6,45	1,14	5,17	2,63
Inmediate logical verbal memory	3,70	2,41	1,54	1,48	7,51	2,53	6,59	2,79	2,91	2,41
Delay logical verbal memory	2,92	2,53	1,33	1,76	7,13	2,70	6,06	2,94	3,16	2,65
Serial verbal learning	6,24	1,70	4,58	3,52	9,25	1,56	8,50	1,94	5,17	3,06
Serial recall	3,90	3,03	2,08	3,34	8,41	1,46	7,28	2,32	4,00	3,22
Cued verbal recall	6,90	3,87	4,50	4,07	11,03	1,11	10,40	1,81	7,33	4,22
Verbal recognition	9,14	2,78	7,42	3,67	11,65	0,68	11,48	0,86	8,67	4,59
Naming	43,57	8,51	32,25	6,32	51,82	5,02	48,09	7,74	34,67	18,30
Semantic Fluency	12,05	5,18	9,75	3,76	18,89	4,88	17,28	4,99	12,00	6,78
Phonological fluency	10,43	4,10	6,17	3,27	15,49	5,19	13,07	4,86	8,83	4,83
Vocabulary	53,19	11,5	38,71	14,50	59,96	13,28	54,34	12,59	66,33	3,51
Analogies	26,06	5,82	20,29	6,62	33,07	7,62	31,94	7,22	39,67	2,08
Matrices	12,00	5,92	7,14	4,88	21,15	9,45	15,81	9,64	26,00	1,00
Block design	16,06	10,4	11,00	11,70	34,82	15,18	29,62	15,51	32,00	7,81
Verbal IQ	89,50	14,4	77,00	12,30	103,53	17,23	96,70	15,87	114,67	6,65
Performance IQ	81,88	10,8	70,86	15,62	101,43	15,36	89,91	15,53	110,33	7,50
Full test IQ	84,38	11,3	74,00	11,15	103,25	15,07	92,77	15,30	113,33	7,50
Digits Span	4,81	1,43	4,40	1,17	5,86	1,29	5,07	1,05	4,00	1,67
Trail making A	86,61	38,4	205,17	144,66	53,08	65,15	66,60	38,30	44,33	32,65
Trail making B	280,81	148,64	354,29	134,51	104,14	43,40	151,59	82,50	211,67	173,71
Delusions	0,31	1,01	2,33	4,12	0,54	1,42	0,77	1,64	0,50	1,00
Hallucinations	0,19	0,544	0,33	0,70	0,35	1,76	0,00	0,00	0,00	0,00
Agitation	1,50	2,33	1,22	2,10	1,08	1,65	1,54	3,57	2,25	2,63
Depression	4,53	3,69	3,00	3,87	1,52	2,18	3,07	2,43	1,40	2,07
Anxiety	4,71	4,75	2,33	2,78	0,71	1,45	1,36	3,24	5,25	4,99
Euphoria/Negation	1,56	3,09	1,44	3,00	0,56	1,41	0,15	0,55	0,00	0,000
Apathy/Indifference	5,71	4,51	2,89	5,18	1,52	3,05	2,00	2,23	3,00	6,00
Disinhibition	1,00	2,033	1,44	3,005	0,24	0,83	0,31	0,63	1,40	1,67
Irritability	4,06	3,924	1,89	1,833	2,21	3,42	1,36	1,55	1,60	2,510
Beck Inventory	16,53	13,422	9,73	6,944	9,72	8,02	20,47	9,63	12,80	8,04

Table 3. Median values and standard deviations calculated for each dementia cause in the elder group.

	FTD		AD		Normal		Depression		PPA	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	72,74	4,06	76,26	5,99	72,93	6,09	71,29	4,85	74,08	6,12
Level of education (years)	10,83	5,46	8,74	4,26	12,14	3,65	10,14	3,97	9,42	2,02
Mini Mental State	24,97	3,79	20,76	4,57	28,59	1,21	27,52	1,90	21,58	5,58
Global CDR	0,84	0,235	0,87	0,21	0,46	0,19	0,51	0,08	0,66	0,24
Direct Span	5,54	1,40	5,06	1,04	5,73	1,282	4,89	1,02	4,58	1,44
Indirect Span	3,29	1,15	2,90	1,00	4,12	0,95	3,66	0,99	2,50	0,79
Clock test	5,26	1,95	3,27	2,81	6,65	0,68	6,15	1,52	3,50	2,93
Inmediate logical verbal memory	4,51	2,68	2,04	1,80	7,630	2,12	6,58	2,37	3,45	2,70
Delay logical verbal memory	3,45	2,95	0,99	1,76	7,278	2,16	6,35	2,59	3,45	2,81
Serial verbal learning	6,20	1,56	4,36	1,78	8,86	1,55	8,14	1,68	5,73	2,83
Serial recall	3,14	2,30	0,95	1,63	7,54	1,87	6,77	2,04	3,64	2,94
Cued verbal recall	6,49	2,91	3,15	2,67	10,29	1,99	10,03	2,28	6,27	4,05
Verbal recognition	9,14	2,37	6,35	2,79	11,71	0,60	11,46	0,98	8,27	4,24
Naming	42,71	7,79	32,71	10,58	50,61	6,27	47,06	7,30	25,75	12,15
Semantic Fluency	12,34	3,76	8,48	3,50	17,50	4,13	15,31	5,75	8,33	5,44
Phonological fluency	9,20	4,22	6,70	3,71	14,25	4,16	11,11	4,96	5,50	3,45
Vocabulary	57,85	11,24	44,37	15,21	59,25	12,62	53,43	14,91	41,75	12,57
Analogies	28,38	9,00	20,78	7,45	33,50	8,27	28,57	9,77	22,75	1,98
Matrices	13,31	9,79	8,71	6,61	19,53	6,16	14,24	7,60	11,38	14,31
Block design	17,54	10,46	14,79	10,54	30,69	14,59	22,90	14,84	19,00	16,51
Verbal IQ	100,68	13,88	87,10	13,42	106,07	18,19	97,62	17,73	81,00	14,72
Performance IQ	88,60	12,16	85,39	10,07	108,07	13,47	92,52	17,79	84,38	10,35
Full test IQ	94,40	12,60	85,04	10,25	109,86	17,02	94,86	17,71	81,75	7,04
Digits Span	5,20	1,23	5,23	1,44	5,79	1,13	4,76	1,06	4,09	1,22
Trail making A	108,85	76,55	153,98	114,59	50,81	17,09	71,21	28,87	139,00	129,99
Trail making B	292,93	158,05	344,97	155,83	127,72	79,68	201,60	114,26	376,25	87,49
Delusions	1,88	3,09	0,69	1,77	0,07	0,26	1,38	3,59	0,13	0,35
Hallucinations	0,42	1,71	0,22	0,86	0,00	0,00	0,00	0,00	0,00	0,00
Agitation	2,94	3,26	1,25	2,22	0,14	0,53	1,00	2,64	0,44	1,33
Depression	3,47	3,89	2,47	2,96	1,00	1,36	3,83	2,94	1,67	2,12
Anxiety	3,22	3,61	1,76	3,08	0,43	0,75	0,09	0,30	0,00	0,000
Euphoria/Negation	1,66	3,61	0,16	0,55	0,21	0,42	0,55	1,29	1,00	1,73
Apathy/Indifference	4,75	4,51	2,63	3,78	0,71	1,85	2,09	3,39	3,25	3,37
Disinhibition	1,88	2,95	0,50	1,72	1,00	3,18	0,70	1,88	1,29	3,40
Irritability	3,72	4,32	2,09	3,20	0,21	0,42	1,75	2,92	2,25	3,41
Beck Inventory	12,64	10,00	9,81	8,95	6,54	3,53	22,66	12,07	18,91	12,60

Table 4. FTD features comparison between younger and elder groups.

	FTD		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)	
	p-Value	*t/U*		65≤	66≥
Mini Mental State	ns	-	ns	,002	-
Global CDR	ns	-	ns	,000	,000
Direct Span	ns	-	ns	ns	-
Indirect Span	ns	-	ns	,001	-
Clock test	ns	-	ns	,000	ns
Inmediate logical verbal memory	ns	-	ns	ns	-
Delay logical verbal memory	ns	-	ns	ns	-
Serial verbal learning	ns	-	ns	,044	-
Serial recall	ns	-	ns	,049	-
Cued verbal recall	ns	-	ns	ns	-
Verbal recognition	ns	-	ns	,018	-
Naming	ns	-	ns	,039	-
Semantic Fluency	ns	-	ns	ns	-
Phonological fluency	ns	-	ns	ns	-
Vocabulary	ns	-	ns	ns	ns
Analogies	ns	-	,025	ns	ns
Matrices	ns	-	ns	,020	,000
Block design	ns	-	ns	,011	,029
Verbal IQ	,018	-2,475	ns	ns	ns
Performance IQ	ns	-	ns	ns	ns
Full test IQ	,035	121,00	ns	ns	,026
Digits Span	ns	-	ns	ns	-
Trail making A	ns	-	ns	ns	-
Trail making B	ns	-	ns	ns	,007
Delusions	,033	180,500	,002	,000	-
Hallucinations	ns	-	,021	,000	-
Agitation	ns	-	ns	,000	-
Depression	ns	-	ns	ns	-
Anxiety	ns	-	,028	,004	-
Euphoria/Negation	ns	-	ns	,000	-
Apathy/Indifference	ns	-	ns	,022	-
Disinhibition	ns	-	ns	,000	-
Irritability	ns	-	ns	ns	-
Beck Inventory	ns	-	,050	,031	-

Table 5. AD features comparison between younger and elder groups.

	AD		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)	
	p-Value	*t/U*		65≤	66≥
Mini Mental State	ns	-	ns	ns	-
Global CDR	ns	-	ns	,000	-
Direct Span	ns	-	ns	ns	-
Indirect Span	ns	-	ns	,000	-
Clock test	ns	-	,005	ns	-
Inmediate logical verbal memory	ns	-	ns	ns	-
Delay logical verbal memory	ns	-	ns	,006	-
Serial verbal learning	ns	-	,002	ns	-
Serial recall	ns	-	,001	,000	-
Cued verbal recall	ns	-	,012	ns	-
Verbal recognition	ns	-	ns	ns	-
Naming	ns	-	ns	ns	-
Semantic Fluency	ns	-	ns	ns	-
Phonological fluency	ns	-	ns	,022	-
Vocabulary	ns	-	ns	ns	-
Analogies	ns	-	ns	ns	-
Matrices	ns	-	ns	ns	-
Block design	ns	-	ns	ns	-
Verbal IQ	ns	-	ns	ns	-
Performance IQ	,002	-3,338	ns	ns	-
Full test IQ	,011	-2,645	ns	ns	-
Digits Span	ns	-	ns	ns	-
Trail making A	ns	-	ns	ns	-
Trail making B	ns	-	ns	ns	-
Delusions	ns	-	,001	,001	-
Hallucinations	ns	-	ns	,000	-
Agitation	ns	-	ns	,001	-
Depression	ns	-	ns	,009	-
Anxiety	ns	-	ns	,002	-
Euphoria/Negation	,050	295,000	,000	,000	-
Apathy/Indifference	ns	-	ns	,000	-
Disinhibition	ns	-	,031	,000	-
Irritability	ns	-	ns	ns	-
Beck Inventory	ns	-	ns	ns	-

Table 6. Normal (control) subjects features comparison between younger and elder groups.

	Normal		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)	
	p-Value	*t/U*		65≤	66≥
Mini Mental State	,026	580,500	ns	-	,006
Global CDR	ns	-	,001	-	,000
Direct Span	ns	-	ns	-	,011
Indirect Span	ns	-	ns	-	,001
Clock test	ns	-	ns	-	,000
Inmediate logical verbal memory	ns	-	ns	-	ns
Delay logical verbal memory	ns	-	ns	-	ns
Serial verbal learning	ns	-	ns	-	,047
Serial recall	,019	2,388	ns	-	ns
Cued verbal recall	ns	-	,001	-	,000
Verbal recognition	ns	-	ns	-	,000
Naming	ns	-	ns	-	,008
Semantic Fluency	ns	-	ns	-	ns
Phonological fluency	ns	-	ns	-	ns
Vocabulary	ns	-	ns	-	ns
Analogies	ns	-	ns	-	ns
Matrices	ns	-	ns	-	ns
Block design	ns	-	ns	-	ns
Verbal IQ	ns	-	ns	-	ns
Performance IQ	ns	-	ns	-	ns
Full test IQ	ns	-	ns	-	ns
Digits Span	ns	-	ns	-	,015
Trail making A	ns	-	ns	-	,004
Trail making B	ns	-	,007	-	,000
Delusions	ns	-	,019	,000	,000
Hallucinations	ns	-	ns	,000	,000
Agitation	ns	-	,000	,000	,000
Depression	ns	-	ns	,000	,000
Anxiety	ns	-	ns	,000	,000
Euphoria/Negation	ns	-	ns	,000	,000
Apathy/Indifference	ns	-	ns	,000	,000
Disinhibition	ns	-	ns	,000	,000
Irritability	ns	-	,000	,000	,000
Beck Inventory	,013	2,526	,005	-	ns

Table 7. Depression features comparison between younger and elder groups.

	Depression		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)	
	p-Value	*t/U*		65≤	66≥
Mini Mental State	ns	-	ns	-	-
Global CDR	,033	-2,170	,010	-	-
Direct Span	ns	-	,018	-	-
Indirect Span	ns	-	ns	-	-
Clock test	ns	-	ns	-	-
Inmediate logical verbal memory	ns	-	ns	-	-
Delay logical verbal memory	ns	-	ns	-	-
Serial verbal learning	ns	-	ns	-	-
Serial recall	ns	-	ns	-	-
Cued verbal recall	ns	-	ns	-	-
Verbal recognition	ns	-	ns	-	-
Naming	ns	-	ns	-	-
Semantic Fluency	ns	-	ns	-	-
Phonological fluency	ns	-	ns	-	-
Vocabulary	ns	-	ns	-	ns
Analogies	ns	-	ns	-	ns
Matrices	ns	-	ns	-	ns
Block design	,042	340,500	ns	-	,006
Verbal IQ	ns	-	ns	-	ns
Performance IQ	ns	-	ns	-	,006
Full test IQ	ns	-	ns	-	ns
Digits Span	ns	-	ns	-	-
Trail making A	ns	-	ns	-	-
Trail making B	,023	-2,313	ns	-	-
Delusions	ns	-	ns	,000	,000
Agitation	ns	-	ns	,000	,000
Depression	ns	-	ns	,009	ns
Anxiety	ns	-	,038	,000	,000
Euphoria/Negation	ns	-	,044	,000	,000
Apathy/Indifference	ns	-	ns	,017	,000
Disinhibition	ns	-	ns	,000	,000
Irritability	ns	-	ns	,007	,001
Beck Inventory	ns	-	ns	-	-

Depressive patients: statistically significant differences were found between age groups in Total CDR, Block design, and Trail making B tests. Elder subjects scored higher in Total CDR and Trail making B tests while younger subjects showed Block design higher scores. See Table **7**.

Table 8. PPA features comparison between younger and elder groups.

	PPA		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)	
	p-Value	*t/U*		65≤	66≥
Mini Mental State	ns	-	ns	,000	ns
Global CDR	ns	-	ns	,000	,000
Direct Span	ns	-	ns	ns	ns
Indirect Span	ns	-	ns	ns	ns
Clock test	ns	-	ns	,014	,034
Inmediate logical verbal memory	ns	-	ns	ns	ns
Delay logical verbal memory	ns	-	ns	ns	ns
Serial verbal learning	ns	-	ns	ns	ns
Serial recall	ns	-	ns	ns	ns
Cued verbal recall	ns	-	ns	ns	ns
Verbal recognition	ns	-	ns	,016	,011
Naming	ns	-	ns	ns	ns
Semantic Fluency	ns	-	ns	ns	ns
Phonological fluency	ns	-	ns	ns	ns
Vocabulary	,010	3,238	ns	ns	ns
Analogies	,000	12,465	ns	ns	ns
Matrices	ns	-	ns	ns	,003
Block design	ns	-	ns	ns	,019
Verbal IQ	,005	3,722	ns	ns	ns
Performance IQ	,012	,000	ns	,000	ns
Full test IQ	,000	6,524	ns	ns	ns
Digits Span	ns	-	ns	,006	,014
Trail making A	,015	9,000	ns	ns	,000
Trail making B	ns	-	ns	ns	,050
Delusions	ns	-	,034	,001	,000
Agitation	ns	-	ns	ns	,000
Depression	ns	-	ns	,023	,030
Apathy/Indifference	ns	-	ns	,001	ns
Disinhibition	ns	-	ns	ns	,000
Irritability	ns	-	ns	,012	,006
Beck Inventory	ns	-	ns	,006	ns

PPA patients: statistically significant differences were found between age groups in Vocabulary, Analogies, Verbal IQ, Performance IQ, Full test IQ and Trail making A tests. Younger subjects showed higher scores in all tests with the only exception of Trail making A test, where elder subjects scored higher. See Table **8**.

In Table **9**, correlations between onset age of behavioral symptoms (assessed through total NPI and its sub-items), cognitive function (measured through MMSE), and mood (scored with Beck Inventory) are summarized. Three statistically significant associations between onset age and dementia symptoms were found: a low and negative association between Euphoria/Negation and onset age, a low

and negative association between Beck inventory and onset age, and a moderate and negative association between MMSE and onset age.

Table 9. Dementia symptoms/onset age correlation.

	Age (Shapiro-Wilk p-Value = ,000)	
	p-Value	**Spearman Rho**
Delusions	ns	-
Hallucinations	ns	-
Agitation	ns	-
Depression	ns	-
Anxiety	ns	-
Euphoria/Negation	,010	-,175**
Apathy/Indifference	ns	-
Disinhibition	ns	-
Irritability	ns	-
MMSE	,000	-,517**
Beck Inventory	,001	-,187**

Different Types of Diseases, their Cognitive and Behavioral Profiles, and Corresponding Relation to Onset Age

One-way ANOVA tests were conducted in order to verify whether statistically significant differences in cognitive and behavioral profiles exist between diagnoses in the younger group. Homoscedasticity was verified by the Levene test. In cases where the subgroups had a small n (<30) and normality assumption was not met the one-way Kruskal-Wallis test was used. This test was also used in cases where neither the assumption of normality not homoscedasticity was met (Table **10**). The post-hoc contrast was Tukey test (Tables **10** and **11**).

One-way ANOVA tests were conducted in order to verify whether statistically significant differences in cognitive and behavioral profiles exist between diagnoses in the elder group. Homoscedasticity was verified by the Levene test. In cases where the subgroups had a small n (<30) and normality assumption was not met the one-way Kruskal-Wallis test was used. This test was also used in cases where neither the assumption of normality not homoscedasticity was met (Table **12**). The post-hoc contrast was Tukey test (Table **13**).

CONCLUSION

AD was the most common cause of dementia in subjects over 65 years old, followed by depression and FTD.

In subjects younger than 65 years old, higher prevalence of cognitively normal and Depressive people was observed, being the most frequently found pathology the degenerative FTD, followed by AD, and finally PPA.

FTD Early Onset *vs* Late-Onset

FTD patients with early onset performanced worse on Verbal IQ and Global IQ. In turn, they had more delusions than late-onset forms.

AD Early-Onset *vs* Late-Onset

Patients with early onset AD performance worse in Performance IQ and the Global IQ and present behavioral disorders such as euphoria and/or denial compared with late onset AD.

Early *vs* Late Cognitively Normal Consulting Subjects

Subjects over 65 year old performanced lower on the MMSE, Serial recall and the Beck Depression Inventory.

Early Onset *vs* Late-Onset Depression

The late-onset depression group had poorer functional performance on CDR, TMT-B, and WASI cubes, and showed a cortical memory decline profile (BSRT memory, BSRT recognition).

PPA Early-Onset *vs* Late-Onset

Subjects with late-onset PPA had worse performance scores on Vocabulary, Analogies, Verbal IQ, Performance IQ, TMT A, and Global IQ.

Early-Onset Dementias: Disorder Type Comparison

Screening Tests

AD patients showed worse scores in the MMSE and the Mini Boston tests compared to FTD subjects. PPA and AD groups showed similar Naming performances. The BSRT revealed lower results in all explored conditions, except in depressive and normal subjects.

Cognitive Assessment

Memory was affected in all conditions AD, FTD, and PPA showing a cortical profile. The Cued Recall Test allowed to distinguish between AD subjects (lower scores), and Depresive and control subjects who performance similarly.

Naming was affected in AD and PPA subjects. Depressive and FTD groups performance similar to normal subjects.

Verbal fluencies (phonological and semantic) were affected in all disorders except depressive and normal subjects.

Regarding WASI test, verbal reasoning (Analogies) was affected in AD and FTD, but results were much lower in AD subjects. The lowest scores in vocabulary, matrices and cubes were obtained in AD patients compared to other groups.

AD and FTD subjects showed greater impairment in Overall IQ, performance IQ, and verbal IQ. The lowest scores were found in AD population.

Table 10. Statistical analysis of cognitive and behavioral profiles between diagnoses in the younger group.

	Young		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)				
	p-Value	*F /X²*		FTD	AD	Normal	Depression	PPA
Mini Mental State	,000	53,016	,000	,002	ns	-	-	,000
TOTAL CDR	,000	76,666	,001	,000	,000	-	-	,000
Span directo	,002	4,560	ns	ns	ns	-	-	ns
Span inverso	,000	34,299	ns	,001	,000	-	-	ns
Clock test	,000	33,178	,000	,000	ns	-	-	,014
Inmediate logical verbal memory	,000	21,474	ns	ns	ns	-	-	ns
Delay logical verbal memory	,000	49,849	ns	ns	,006	-	-	ns
Serial verbal learning	,000	49,517	,001	,044	ns	-	-	ns
Serial recall	,000	56,900	,000	,049	,000	-	-	ns
Cued verbal recall	,000	44,666	,000	ns	ns	-	-	ns
Verbal recognition	,000	39,545	,000	,018	ns	-	-	,016
Naming	,000	49,911	,000	,039	ns	-	-	ns
Semantic Fluency	,000	14,839	ns	ns	ns	-	-	ns
Phonological fluency	,000	39,081	ns	ns	,022	-	-	ns
Vocabulary	,001	5,175	ns	ns	ns	-	-	ns
Analogies	,000	8,139	ns	ns	ns	-	-	ns
Matrices	,000	27,697	ns	,020	ns	-	-	ns
Block design	,000	27,045	ns	,011	ns	-	-	ns
Verbal IQ	,000	6,395	ns	ns	ns	-	-	ns
Performance IQ	,000	32,072	ns	ns	ns	-	-	,000
Full test IQ	,000	10,965	ns	ns	ns	-	-	ns
Digits Span	,000	24,886	ns	ns	ns	-	-	,006
Trail making A	,000	43,168	,000	ns	ns	-	-	ns
Trail making B	,000	41,133	,000	ns	ns	-	-	ns
Delusions	ns	-	,001	,000	,001	,000	,000	,001
Hallucinations	ns	-	ns	,000	,000	,000	-	-
Agitation	ns	-	ns	,000	,001	,000	,000	ns
Depression	,038	10,170	ns	ns	,009	,000	,009	,023
Anxiety	,001	19,141	,000	,004	,002	,000	,000	ns
Euphoria/Negation	ns	-	,011	,000	,000	,000	,000	-
Apathy/Indifference	,004	15,119	,010	,022	,000	,000	,017	,001
Disinhibition	ns	-	,003	,000	,000	,000	,000	ns
Irritability	ns	-	,011	ns	ns	,000	,007	,012
Beck Inventory	,000	39,996	,007	,031	ns	-	,013	,006

Table 11. Post-hoc comparisons: same letters indicate same subset.

	FTD	AD	Normal	Depression	PPA
Mini Mental State	26,10 BC	20,50 A	29,05 C	28,26 C	24,00 B
Global CDR	0,90 C	0,90 C	0,36 A	0,45 AB	0,58 B
Direct Span	5,10 AB	4,82 AB	5,92 B	5,16 AB	4,00 A
Indirect Span	2,85 A	2,64 A	4,27 B	3,66 AB	3,00 A
Clock test	5,10 AB	4,00 A	6,61 B	6,45 B	5,17 AB
Inmediate logical verbal memory	3,70 A	1,54 A	7,51 B	6,59 B	2,91 A
Delay logical verbal memory	2,92 A	1,33 A	7,13 B	6,06 B	3,16 A
Serial verbal learning	6,24 A	4,58 A	9,25 B	8,50 B	5,17 A
Serial recall	3,90 A	2,08 A	8,41 B	7,28 B	4,00 A
Cued verbal recall	6,90 B	4,50 A	11,03 C	10,40 C	7,33 B
Verbal recognition	9,14 A	7,42 A	11,65 B	11,48 B	8,67 A
Naming	43,57 B	32,25 A	51,82 C	48,09 BC	34,67 A
Semantic Fluency	12,05 A	9,75 A	18,89 B	17,28 B	12,00 A
Fluencia fonológica	10,43 AB	6,17 A	15,49 C	13,07 BC	8,83 AB
Vocabulary	53,19 AB	38,71 A	59,96 B	54,34 AB	66,33 B
Analogies	26,06 AB	20,29 A	33,07 BC	31,94 BC	39,67 C
Matrices	12,00 AB	7,14 A	21,15 BC	15,81 ABC	26,00
Block design	16,06 AB	11,00 A	34,82 B	29,62 AB	32,00 B
Verbal IQ	89,50 AB	77,00 A	103,53 BC	96,70 ABC	114,67 C
Performance IQ	81,88 AB	70,86 A	101,43 BC	89,91 AB	110,33 C
Full test IQ	84,38 AB	74,00 A	103,25 BC	92,77 AB	113,33 C
Digits Span	4,81 AB	4,40 A	5,86 B	5,07 AB	4,00 A
Trail making A	86,61 A	205,17 B	53,08 A	66,60 A	44,33 A
Trail making B	280,81 CD	354,29 C	104,14 A	151,59 AB	211,67 BC
Delusions	-	-	-	-	-
Hallucinations	-	-	-	-	-
Agitation	-	-	-	-	-
Depression	Groups did not differ in post-hoc analysis				
Anxiety	4,71 AB	2,33 AB	0,71 A	1,36 AB	5,25 B
Euphoria/Negation	-	-	-	-	-
Apathy/Indifference	Groups did not differ in post-hoc analysis				
Disinhibition	-	-	-	-	-
Irritability	-	-	-	-	-
Beck Inventory	16,53 AB	9,73 A	9,72 A	20,47 B	12,80 AB

Attention, measured through TMT-A, was affected in all groups except in AD.

Cognitive flexibility, assessed by TMT-B, provided poor results in all groups except normal one.

Table 12. Statistical analysis of cognitive and behavioral profiles between diagnoses in the elder group.

	Elder		Levene p-Value	Shapiro-Wilk p-Value (Valid for Small n)				
	p-Value	*F /X²*		FTD	AD	Normal	Depression	PPA
Mini Mental State	,000	99,172	,000	-	-	,006	-	ns
Global CDR	,000	86,039	,000	,000	-	,000	-	,000
Span directo	,008	13,915	,018	-	-	,011	-	ns
Span inverso	,000	10,501	ns	-	-	,001	-	ns
Clock test	,000	53,972	,000	-	-	,000	-	,034
Inmediate logical verbal memory	,000	101,803	,005	-	-	ns	-	ns
Delay logical verbal memory	,000	114,924	,000	-	-	ns	-	ns
Serial verbal learning	,000	105,619	,042	-	-	,047	-	ns
Serial recall	,000	127,769	,007	-	-	ns	-	ns
Cued verbal recall	,000	111,029	,003	-	-	,000	-	ns
Verbal recognition	,000	114,440	,000	-	-	,000	-	,011
Naming	,000	91,692	,003	-	-	,008	-	ns
Semantic Fluency	,000	83,938	,002	-	-	ns	-	ns
Phonological fluency	,000	23,637	ns	-	-	ns	-	ns
Vocabulary	,000	6,922	ns	ns	-	ns	ns	ns
Analogies	,000	31,027	,011	ns	-	ns	ns	ns
Matrices	,000	27,890	ns	,000	-	ns	ns	,003
Block design	,000	18,082	ns	,029	-	ns	,006	,019
Verbal IQ	,000	8,099	ns	ns	-	ns	ns	ns
Performance IQ	,000	24,886	ns	ns	-	ns	,006	ns
Full test IQ	,000	30,004	,002	,026	-	ns	ns	ns
Digits Span	,001	19,030	ns	-	-	,015	-	,014
Trail making A	,000	50,536	,000	-	-	,004	-	,000
Trail making B	,000	45,946	,000	,007	-	,000	-	,050
Delusions	,024	11,248	,000	-	-	,000	,000	,000
Hallucinations	ns	-	,013	-	-	-	-	-
Agitation	,000	22,627	,000	-	-	,000	,000	,000
Depression	ns	-	,001	-	-	,000	ns	,030
Anxiety	,000	20,402	,000	-	-	,000	,000	-
Euphoria/Negation	ns	-	,000	-	-	,000	,000	,001
Apathy/Indifference	,007	14,233	,004	-	-	,000	,000	ns
Disinhibition	,034	10,445	,003	-	-	,000	,000	,000
Irritability	,009	13,425	,000	-	-	,000	,001	,006
Beck Inventory	,000	44,935	,000	-	-	ns	-	ns

Table 13. Post-hoc comparisons: same letters indicate same subset.

	FTD	AD	Normal	Depression	PPA
Mini Mental State	24,97 B	20,76 A	28,59 C	27,52 BC	21,58 A
Global CDR	0,84 B	0,87 B	0,46 A	0,51 AB	0,66 B
Direct Span	5,54 B	5,06 AB	5,73 B	4,89 AB	4,58 A
Indirect Span	3,29 B	2,90 AB	4,12 C	3,66 BC	2,50 A
Clock test	5,26 BC	3,27 A	6,65 C	6,15 C	3,50 AB
Inmediate logical verbal memory	4,51 B	2,04 A	7,63 C	6,58 C	3,45 AB
Delay logical verbal memory	3,45 B	0,99 A	7,27 C	6,35 C	3,45 B
Serial verbal learning	6,20 B	4,36 A	8,86 C	8,14 C	5,73 B
Serial recall	3,14 B	,95 A	7,54 C	6,77 C	3,64 B
Cued verbal recall	6,49 B	3,15 A	10,29 C	10,03 C	6,27 B
Verbal recognition	9,14 B	6,35 A	11,71 C	11,46 C	8,27 B
Naming	42,71 B	32,71 A	50,61 C	47,06 BC	25,75 A
Semantic Fluency	12,34 B	8,48 A	17,50 C	15,31 BC	8,33 A
Phonological fluency	9,20 BC	6,70 AB	14,25 D	11,11 C	5,50 A
Vocabulary	57,85 B	44,37 A	59,25 B	53,43 AB	41,75 A
Analogies	28,38 ABC	20,78 A	33,50 C	28,57 BC	22,75 AB
Matrices	13,31 AB	8,71 A	19,53 B	14,24 AB	11,38 A
Block design	17,54 A	14,79 A	30,69 B	22,90 AB	19,00 A
Verbal IQ	100,68 BC	87,10 AB	106,07 C	97,62 BC	81,00 A
Performance IQ	88,60 A	85,39 A	108,07 B	92,52 A	84,38 A
Full test IQ	94,40 B	85,04 AB	109,86 C	94,86 B	81,75 A
Digits Span	5,20 BC	5,23 BC	5,79 C	4,76 AB	4,09 A
Trail making A	108,85 ABC	153,98 C	50,81 A	71,21 AB	139,00 BC
Trail making B	292,93 BC	344,97 C	127,72 A	201,60 AB	376,25 C
Delusions	Groups did not differ in post-hoc analysis				
Hallucinations	-	-	-	-	-
Agitation	2,94 B	1,25 AB	,14 A	1,00 AB	0,44 A
Depression	-	-	-	-	-
Anxiety	3,22 B	1,76 AB	,43 AB	0,09 A	0,00 A
Euphoria/Negation	-	-	-	-	-
Apathy/Indifference	4,75 B	2,63 AB	0,71 A	2,09 AB	3,25 AB
Disinhibition	Groups did not differ in post-hoc analysis				
Irritability	3,72 B	2,09 AB	0,21 A	1,75 AB	2,25 AB
Beck Inventory	12,64 AB	9,81 A	6,54 A	22,66 B	18,91 BC

Behavioral Assessment

No statistically significant differences were observed between groups. A tendency to increased anxiety in FTD and PPA, and major depression in the depressive group, FTD and PPA was noted.

Late-Onset Dementias: Disorder Type Comparison

Screening Tests

The MMSE and the clock test results were altered in AD and PPA subjects, the last ones obtaining the lowest scores. FTD and depressive patients performance similar to cognitively healthy control subjects.

Cognitive Assessment

Memory was severely affected in the AD group, presenting with a cortical profile. FTD and PPA subjects performance similar, while the depression group score similar to normal subjects.

Naming test results were decrease in AD subjects and especially lowered in PPA. Depressive and FTD subjects performance similar, but different from normal control group.

Verbal fluencies (phonological and semantic) were diminished mostly in AD and PPA, while in depressive and FTD groups, results were similar but lower and different from normal one.

Regarding WASI test, verbal reasoning (Analogies) and vocabulary scores were more affected in PPA and AD, compared to other groups. The Matrices and cubes tests showed lower scores in AD subjects.

Verbal IQ present the lowest scores in the PPA group, and then in AD with a similar statistical pattern.

Executive IQ scored low in FTD, AD, PPA and depressive groups. Overall IQ results were most affected in the PPA and AD group.

Attention, as measured by TMT-A, was affected in all groups compared to normal subjects.

Cognitive flexibility, assessed by TMT-B, performance worst in AD and PPA groups.

Behavioral Assessment

Agitation occurred in all groups, except in PPA where it showed a similar behavior to normal group.

Increased anxiety was observed in FTD subjects; apathy and indifference was also higher in the FTD group, but in AD, depressive, and PPA subjects scores were similar to normal ones.

Irritability presence was greater in FTD subjects and similar in AD, depressive and PPA groups.

Depression measured by self-administered questionnaires, was higher in Depressive and PPA groups.

Depression was greater in PPA subjects respect to FTD ones, and lower in the AD.

Correlations

Three statistically significant associations were found with onset age:

At younger onset age, greater severity of cognitive impairment (assessed by global cognition tests such as the MMSE), behavioral impairment (with more euphoria/denial symptoms reported by the family through the NPI questionnaire) and major depression (self-scored by patients through the Beck inventory) were observed.

Diagnostic and Therapeutic Approach

Patients with dementia universally present with psychiatric and behavioral symptoms. These neuropsychiatric symptoms (NPS) seem to be more aggressive in early onset dementias. However, specific available NPS therapeutic choices and pharmacological interventions tend to be the same at all ages.

Many of the young-onset dementias may be potentially reversible so diagnostic efforts and early characterization must be pursued to identify their underlying causes. Depression, drug or alcohol abuse, nutritional conditions like vitamin B-12 deficiency, space-occupying lesions, normal pressure hydrocephalus, infections (venereal diseases), or metabolic conditions like hypothyroidism or diabetes, are common causes of reversible dementias. Specific treatment of underlying causes can halt the cascade of events that lead to irreversible brain lesions.

Patients with NPS at any age should be evaluated through a careful medical history including cognitive and functional status, presence of co-morbidities, family history, present prescribed and non-prescribed medications, sleep patterns, and social and environmental aspects. Information given by family members and caregivers is also important to establish the relevance of cognitive/functional changes observed in patients with NPS.

Physical examination, laboratory tests, neuropsychological test batteries, and structural or functional images of the brain could be also necessary. Correlations between intracerebral pathology and early dementia symptoms can be established through new technologies based on biomarkers. Intracerebral amyloid molecular imaging with PET and dosage of amyloid-beta peptide and hyperphosphorylated tau protein in cerebrospinal fluid samples are new diagnostic alternatives that allow differentiate reversible causes of dementia from neurodegenerative processes like AD or FTD.

Discarded and specifically treated all identified underlying causes of dementias might not help control NPS. For these cases, a wide variety of pharmacologic agents are used in the management of psychiatric and behavioral symptoms.

Dillon *et al*. have recently revised the reported NPS related to prodromal stages of dementia and their neuroanatomical correlations [5]. These authors also state that a variety of pharmacologic agents are used in the management of psychiatric and behavioral symptoms in dementia; for example, cholinesterase inhibitors, N-methyl-D-aspartate (NMDA), antipsychotics, atypical antipsychotics risperidone and olanzapine, antidepressants, and other drugs (benzodiazepines, mood stabilizers, non-benzodiazepine hypnotics). Despite this, pharmacologic therapies are not particularly effective [5].

Being AD the leading cause of dementia, many therapeutic strategies have been developed and several trials are ongoing targeting different aspects of AD pathophysiology. Recently, Ling-Yun Fan and Ming-Jan Chiu have revised the current concepts and future strategies of combinated therapies for AD [10]. Most extended treatment for AD is combination of a cholinesterase inhibitor (donepezil, rivastigmine, and galantamine) and memantine. Nowadays, a big body of clinical research focuses on the amyloid cascade which is believed to be responsible for the degenerative changes and cognitive/behavioral decline typically observed in AD. Passive immunization with monoclonal antibodies (bapineuzumab, solanezumab, gantenerumab, crenezumab) is suggested to remove amyloid from the brain throught different proposed mechanism of action [11]. Other

treatment strategies are Tau-centered since neurofibrillary tangles are another hallmark of the pathological findings in AD brains. Mitochondrial-targeted therapies have been proposed for patients carrying amyloid precursor protein (*APP*) and presenilin-1 and presenilin-2 (*PSEN1* and *PSEN2*) mutant genes and antioxidants like omega-3, polyunsaturated fatty acids, vitamin E, statins, *G. bilova*, vitamin B12, folate, and curcumin are additional potential strategies [10]. A patented combination of nutrients which includes omega-3 fatty acids, choline, uridine monophosphate and a mixture of antioxidants and B vitamins (Souvenaid®) is a medical nutrition product designed to support synapse formation and function in early Alzheimer's disease. Omega-3 polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid), uridine (as uridine monophosphate) and choline are nutritional precursors required for synaptic membrane phospholipid synthesis [12]. Phosphodiesterase inhibitors, thiazolidinedione, nerve growth factors (Cerebrolysin®) and 5-HT6 receptor antagonists have also been summarized in Ling-Yun Fan and Ming-Jan Chiu review as potential combination strategies and ongoing trials [10].

Proposed non-pharmacological interventions include environmental modifications, recreation, and music therapies as well as transcranial magnetic stimulation, and cognitive training and rehabilitation [10].

Each pharmacologic and non-pharmacologic intervention should be tailored to the specific symptoms of each individual patient, and decisions about the type and duration of treatments should be based on their efficacy and patients' tolerance. A multidisciplinary health team is fundamental to the optimal management of patients with NPS and cognitive impairment [5].

DISCUSSION

The present work shows that the onset age of cognitive and/or behavior impairments may be one of the variables influencing the clinical heterogeneity of the disorders described herein. Different mechanisms have been proposed that could be related to this variability, as the coexistence of other neurodegenerative disorders, individual vulnerability differences in response to injury from a degenerative disease, temporary differences in cumulative injury phenomenon, educational level, presence of certain environmental factors and the combination of several of them.

The lower IQ found in early onset dementia patients could correspond to a reduced cognitive reserve, being this one a potentially modifiable risk factor for the onset of the disease.

In the new era of biomarkers, their help in identifying each clinical phenotype could encourage their employ in clinical practice and increase their use as an assist in selecting more accurate pharmacological treatment for dementias.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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