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Phenotypic expressions of Alzheimer's disease: a gender perspective

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Summary. *Introduction.* Dementia is one of the main diseases linked to aging and leading to disability. The gender perspective of this disease has not been studied in a complete and dedicated way and this constitutes a great limitation because dementia, like other diseases, appears to have a gender-related expression. The aim of this research is to contribute to the study of gender differences in a large cohort of patients affected by Alzheimer's disease. *Methods and patients.* The study population included the clinical records of 1925 patients with Alzheimer's disease, diagnosed according to NINCDS-ADRDA criteria and to NIA-AA, from the e-database of the Neurogenetic Regional Centre (NRC) of Lamezia Terme (Southern Italy). The mean age of the sample was 71.5 ± 8.9 years and follow-up was an average of 4 years. The variables included in the analysis and differentiated for gender were the prevalence and the onset of the disease, the time elapsed between the onset and the first consultation, duration of follow-up, duration of the disease, education, cardiovascular and metabolic risk factors. A check list of symptoms and signs was compiled from the cognitive and behavioral history and categorized in 12 clusters. Statistical analysis was performed using IBM SPSS 20 (significance was given by $p < 0.05$). *Results.* Women were more numerically represented in the sample (67.1%). There were no differences according to gender in the time elapsed between onset of symptoms and the first consultation, in the follow-up period and in the duration of disease. Women were more cognitively impaired at baseline (MMSE score 15.9 ± 5.9 vs 17 ± 6.5), had a lower level of education (5.6 years vs 6.51 years) and presented higher comorbidity and incidence of depression ($p = 0.000$) and anxiety ($p = 0.002$). Men displayed a more rapid decline at the end of the follow-up, losing 3.85 ± 4.66 points vs 2.93 ± 4.39 at MMSE; they showed a statistically significant prevalence in behavioral symptoms ($p = 0.009$), including irritability ($p = 0.000$) and agitation ($p = 0.041$), and some cognitive deficits, such as language impairments ($p = 0.000$), apraxia ($p = 0.005$), spatial disorientation ($p = 0.006$) and acalculia ($p = 0.035$). APOE results were not representative in terms of gender differences but confirmed a possible impact of the ε4 allele on cognitive decline. *Discussion.* Behind the classical memory impairment and temporal disorientation, that are present in about all men and woman, a different AD phenotype between the two genders emerges from this work. Our results revealed a poorly-educated female sample, with a worse cognitive impairment and mood disorders. Men showed a more rapid cognitive impairment and an aggressive behavioral picture. The identification of specific gender aspects, cognitive and behavioral, could be a valuable aid for a faster identification of Alzheimer's disease and its better management.

Key words: Alzheimer's disease, gender-specific medicine.

Espressioni fenotipiche della malattia di Alzheimer: una prospettiva di genere

Riassunto. *Introduzione.* La demenza è una delle principali patologie connesse all'invecchiamento e una delle maggiori cause di disabilità. Tuttavia, gli studi sulle differenze di genere non sono stati ancora sviluppati in maniera completa sebbene esistano indicazioni di quadri clinici diversamente espressi nei due sessi. Lo scopo di questo lavoro è stato quello di analizzare le differenze di genere in un'ampia coorte di pazienti affetti da malattia di Alzheimer. *Metodi e pazienti.* Il campione è costituito da 1925 pazienti affetti da malattia di Alzheimer (diagnosticata secondo i criteri NINCDS-ADRDA e NIA-AA) e seguiti presso il Centro Regionale di Neurogenetica di Lamezia Terme (Calabria, Sud Italia). L'età media è di 71,5 ± 8,9 anni ed il follow-up medio è di 4 anni. Le variabili considerate sono state: prevalenza ed esordio della malattia, tempo intercorso tra esordio e prima visita, durata del follow-up e della malattia, scolarità, fattori di rischio cardiovascolari e metabolici oltre a un elenco di segni e sintomi che sono stati estratti dall'anamnesi cognitiva e comportamentale dei pazienti e suddivisi in 12 cluster. L'analisi statistica è stata effettuata mediante SPSS 20 ($p < 0,05$). *Risultati.* Il sesso femminile è maggiormente rappresentato nel campione (67,1%). Non sono risultate differenze significative nel tempo intercorso tra l'esordio della malattia e la prima visita, nella durata del follow-up e nella durata della malattia. Le donne presentano una maggiore compromissione cognitiva sia alla valutazione basale che al termine del follow-up (MMSE 15,9 ± 5,9 vs 17 ± 6,5 nei maschi, che presentano un declino cognitivo più rapido alla fine del periodo di valutazione: MMSE 3,85 ± 4,66 vs 2,93 ± 4,39 nelle donne). Le donne della popolazione da noi studiata presentano una scolarità più bassa (5,6 anni vs 6,51), un maggiore indice di comorbilità e una più alta prevalenza di ansia ($p = 0,002$) e depressione ($p = 0,000$). Gli uomini si presentano con una prevalenza statisticamente più elevata di disturbi comportamentali, tra cui irritabilità ($p = 0,000$) e agitazione ($p = 0,041$), e diversi disturbi cognitivi, tra cui deficit di linguaggio ($p = 0,000$), aprassia ($p = 0,005$), disorientamento spaziale ($p = 0,006$) e acalculia

(p = 0,035). I risultati relativi alla distribuzione dell'allele ε4 dell'APOE non mostrano differenze significative in relazione al genere, sebbene confermino un possibile impatto di questo allele sul declino cognitivo. *Discussione.* Oltre al classico pattern alzheimeriano caratterizzato dal disturbo di memoria e dal disorientamento temporale, presente in quasi tutto il campione senza differenza di genere, le donne si presentano con una più bassa scolarità e un più grave declino cognitivo, e con la maggiore prevalenza di disturbi del tono dell'umore. Diversamente, gli uomini mostrano un più rapido declino cognitivo e un quadro comportamentale più aggressivo. L'identificazione di specifici aspetti di genere potrebbe essere un valido aiuto per un'identificazione più precoce della malattia di Alzheimer e una sua migliore gestione.

Parole chiave: malattia di Alzheimer, medicina genere-specifica.

Introduction

Populations are globally getting older and women will live longer than men but this means more years spent in ill health. Men have a shorter life expectancy than women, but they enjoy a greater proportion of their lives in good health[1]. Dementia is one of the major diseases linked to aging that lead to disability and Alzheimer's disease (AD) is, almost globally, the most prevalent one of these. In recent years, AD detection and its early diagnosis have improved with NIA-AA criteria[2], though unfortunately, this has not yet corresponded to a great (and expected) advancement in pharmacological treatments. It is well known that the gender perspective has not properly enriched the dementia research world: data is inconsistent, frequently inferred from other research projects having other aims and analyzing different contexts and different set populations, not specifically produced and dedicated. This is a great limitation, important to overcome, because the different types of dementia, like other diseases, also seem to show a gender-related expression. The Italian epidemiological study on Aging (ILSA) conducted by CNR reported a greater prevalence of AD in women and vascular dementia in males[3]; Lewy body disease is greatly expressed in cortical brain[4] of males and the same gender trend has been signaled for Parkinson disease (PD) dementia[5].

A recent revision work[6], reconfirms that AD is preferentially expressed in women, while Parkinson's disease, Lewy body dementia and vascular dementia are more frequent in males.

The aim of this work is to contribute to this topic, analyzing gender differences in a large cohort of patients affected by Alzheimer's disease, by evaluating qualitative and quantitative clinical features such as onset, progression, phenotypic picture, duration and associated risk factors.

Patients and methods

The dataset included 1925 patients diagnosed by AD and followed at the Neurogenetic Regional Centre (NRC) in Lamezia Terme (ASP CZ) from 1996 to 2016.

Diagnosis was performed according to NINCDS-ADRDA criteria[7] and to the National Institute on Aging and Alzheimer's Association workgroup[2]. The mean age of the whole sample was 71.5 ± 8.9 years. Follow-up was mean 4 years. Duration of the disease was about 9 years. Most of the patients came from southern Italy. Data was retrospectively extracted from corresponding clinical records.

For each patient we calculated: onset of the disease (derived from the clinical history and reported by informant) defined as the time when the patient presented with evident cognitive and/or behavioural disorders; familial recurrence (at least one first-degree relative affected); time elapsed between the onset and the first visit; follow-up duration. Education (low ≤5 years, high >5 years) was analyzed continuously and by levels. Cardiovascular risk factors (hypertension, heart diseases, hypercholesterolemia, diabetes), dysthyroidism and psychiatric disturbances were considered positive when reported in the patient's medical history.

APOEε4+ genotype and allelic frequency was calculated from a sample of 912 patients.

Mini Mental State Examination (MMSE)[8]; Activities of Daily Living (ADL)[9] and Instrumental Activities of Daily Living (IADL)[10], Cumulative Illness Rating Scale (CIRS)[11] and Hachinski[12] were performed on all patients.

A checklist encompassing cognitive and behavioral symptoms and signs collected through medical history or ascertained by the medical team was then implemented and subdivided into twelve clusters as shown in Table 1.

Statistical analysis

Student T-test was used to compare the mean value of the answers to the tests and the χ^2 to evaluate the differences among risk factors and clinical signs between men and women. All analyses were performed on the whole group and differentiated by gender. To understand whether the results are stable over time, the whole period under examination was divided into two decades (1996-2005 and 2006-2016). Statistical significance was given by $p < 0.05$. All analyses were performed by SPSS 21 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Women were 67.1% of the total AD and were much more copiously represented in the late onset form whereas males were significantly prevalent in the early

Table 1. Checklist encompassing cognitive and behavioral symptoms and signs collected through medical history or ascertained by the medical team.

CLUSTERS		
Orientation	Time and space disorientation	
Memory disorders	Masking and memory disturbances	
Speech disorders	Phonemic and semantic paraphasias	Semantic aphasia
	Absence of language	Verbal initiative reduction
	Palilalia	Echolalia
	Dysphasia	Dysarthria
	Sensory aphasia	Aphasia nominum
	Vocal stereotypies	
Agnosia	Agnosia	Mirror sign
	Prosopagnosia	Color recognition disorder
Apraxia	Constructive apraxia	Ideomotor apraxia
	Dressing apraxia	Ideational apraxia
Planning	Planning disorders	Programming deficit
	Attention deficit	Abstraction deficit
Graphia and calculation	Agraphia and dysgraphia	Acalculia
	Dyslexia	
Sleep disorders		
Behavioral disorders	Irritability	Perseveration
	Poor personal hygiene	Impulsivity
	Disinhibition	Social isolation
	Loss of social awareness	Mental rigidity
	Apathy	Aggressiveness
	Hyperactivity	Sexual behavior disorders
	Bulimia	Wandering
Mood disorders	Hypochondria	Affective disorders
	Anxiety	Reduction of social interest
	Depression	
Psychosis	Hallucinations	Illusions
	Obsessive ideas	Agitations
Sphincter disorders		

onset group (p = 0.008) (Table 2). No differences in familial recurrence emerged in relation to gender.

Elapsing time between the onset of the disease and the first visit (*Elapsing Time Onset-Visit*) was about 4 years without gender difference (men 3.7 ± 3.3 years, women 3.7 ± 3.1 years) over the whole period (Table 2). However, patients assessed between 2006 and 2016 had a statistically significant lower *Elapsing Time Onset-Visit* than those assessed between 1996 and 2005 (p = 0.001) (Table 3).

The mean follow-up calculated on a smaller sample (431 men and 944 women) did not reveal significant differences: both groups were followed up for the same time with an average follow-up of about 4 years (men 3.3 ± 2.7 years, women 3.5 ± 2.9 years) (Table 2).

Education: the men had received more education than women (6.5 ± 4.5 yrs and 5.1 ± 4.1 yrs respectively, p = 0.000). A lower education level was more prevalent in late onset AD female group (p = 0.000) (Table 2) (Figure 1).

At the first evaluation of cognitive impairment the MMSE score was 16.3 ± 6.2 and women appeared more compromised than men (MMSE 15.9 ± 5.9 vs 17 ± 6.5

Table 2. Baseline characteristics in the two groups.

	Male (n=633) 32.9%	Female (n=1292) 67.1%	p_value
Onset, (years)*	70.9±9.0	71.8±8.8	ns
Early, no. (%)	149 (23.5)	238 (18.4)	*0.008*
Late, no. (%)	484 (76.5)	1054 (81.6)	
Familiarity, no. (%)	332 (52.4)	656 (50.8)	ns
ETOV, (years)*	3.7±3.3	3.7±3.1	ns
Follow-up, (years)*	3.3±2.7	3.5±2.9	ns
Education, (years)*	6.5±4.5	5.1±4.1	*0.000*
Low, no. (%)	364 (63.5)	930 (73.1)	*0.000*
High, no. (%)	209 (36.5)	477 (26.9)	
MMSE baseline*	17.0±6.5	15.9±8.8	*0.001*
MMSE at the 4 yrs follow-up*	15.2±6.0	14.0±5.8	ns

* Data is expressed as mean ± standard deviation (SD).
MMSE: Mini Mental State Examination; ETOV: elapsing time onset-visit.

Table 3. Baseline characteristics in the two decades.

	First period 1996-2005 (n=458) 23.8%	Second period 2006-2016 (n=1467) 76.2%	p_value	First period			Second period		
				Male	Female	p_value	Male	Female	p_value
ETOV, (years)*	4.2±3.3	3.6±3.2	*0.001*	4.2±3.2	4.2±3.3	ns	3.6±3.4	3.6±3.1	ns
Education, (years)*	5.4±3.9	5.6±4.4	ns	6.3±4.1	4.9±3.8	*0.002*	6.6±4.7	5.1±4.2	*0.000*
Low, no. (%)	267 (75.6)	1027 (72.4)	ns	78 (65%)	189 (81.1%)	*0.001*	286 (63.1%)	741 (76.8%)	*0.000*
High, no. (%)	86 (24.4)	391 (27.6)		42 (35%)	44 (18.9%)		167 (36.9%)	224 (23.2%)	
MMSE baseline*	14.0±7.0	16.9±5.8	*0.000*	14.9±7.5	13.6±6.7	ns	17.7±6.1	16.6±5.5	*0.003*

* Data is expressed as mean ± standard deviation (SD).
ETOV: elapsing time onset-visit; MMSE: Mini Mental State Examination.

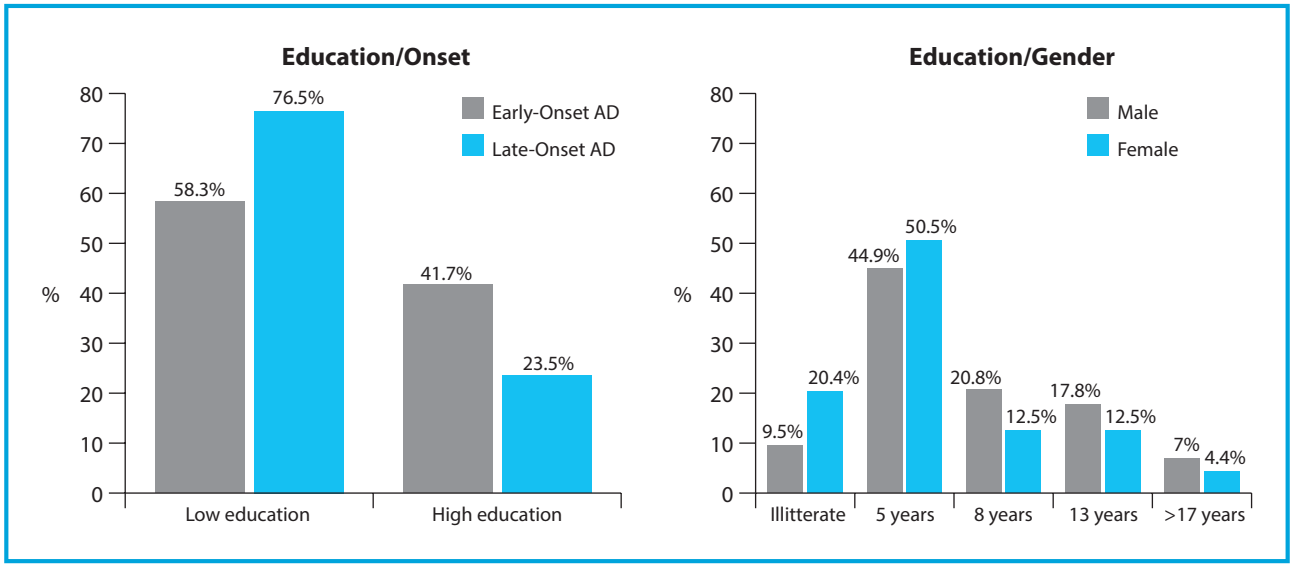

Figure 1. Education by onset and gender.

Table 4. Prevalence of risk factors in the two groups.

	Male (n=633) 32.9%	Female (n=1292) 67.1%	p_value
Alcohol, no. (%)	47 (7.4)	11 (0.9)	*0.000*
Dystyroidism, no. (%)	39 (6.2)	269 (20.8)	*0.000*
Cardiopathy, no. (%)	169 (26.7)	307 (23.8)	ns
Hypercholesterolemia, no. (%)	182 (28.8)	473 (36.6)	*0.001*
Hypertriglyceridemia, no. (%)	76 (12)	178 (13.8)	ns
Hypertension, no. (%)	305 (48.2)	755 (58.4)	*0.000*
Diabetes, no. (%)	100 (15.8)	210 (16.3)	ns
Depression no. (%)	64 (10.1)	212 (16.4)	*0.000*
ApoE alleles	Frequency (%±SE) 296	Frequency (%±SE) 616	
ε2	21 (3.2±0.7)	49 (4.2±0.6)	
ε3	489 (75.2±1.7)	867 (73.9±1.3)	ns
ε4	140 (21.6±1.6)	258 (21.9±1.2)	

SE: standard error.

Table 5. Symptoms and signs in the two groups.

	Male (n=633) 32.9%	Female (n=1292) 67.1%	p_value
Sphincter disorders, no. (%)	112 (17.7)	243 (18.8)	ns
Sleep disorders, no. (%)	180 (28.4)	323 (25.0)	ns
Psychosis, no. (%)	291 (46.0)	571 (44.2)	ns
Mood disorder, no. (%)	202 (31.9)	541 (41.9)	*0.000*
Graphia and calculation, no. (%)	115 (18.2)	175 (13.5)	*0.009*
Planning, no. (%)	199 (31.4)	438 (33.9)	ns
Apraxia, no. (%)	226 (35.7)	398 (30.8)	*0.035*
Agnosia, no. (%)	176 (27.8)	351 (27.2)	ns
Loss of memory, no. (%)	577 (91.2)	1211 (93.7)	ns
Spatial orientation deficit, no. (%)	397 (62.7)	724 (56.0)	*0.006*
Temporal orientation deficit, no. (%)	394 (62.2)	835 (64.6)	ns
Impairment of language, no. (%)	295 (46.6)	475 (36.8)	*0.000*
Sensory aphasia, no. (%)	62 (9.8)	88 (6.8)	*0.028*
Semantic paraphasias, no. (%)	25 (3.9)	24 (1.9)	*0.01*
Word aphasia, no. (%)	174 (27.5)	279 (21.6)	*0.005*
Behavioral disorders, no. (%)	396 (62.6)	729 (56.4)	*0.012*
Agitation, no. (%)	182 (28.8)	314 (24.3)	*0.041*
Depression, no. (%)	136 (21.5)	406 (31.4)	*0.000*
Irritability, no. (%)	229 (36.2)	344 (26.6)	*0.000*
Aggression, no. (%)	153 (24.2)	191 (14.8)	*0.000*
Alteration of sexual behavior, no. (%)	11 (1.7)	0 (0.0)	*0.000*
Mental rigidity, no. (%)	16 (2.5)	15 (1.2)	*0.041*
Disinhibition, no. (%)	70 (11.1)	96 (7.4)	*0.01*
Bulimia, no. (%)	59 (9.3)	65 (5.0)	*0.000*
Apathy, no. (%)	241 (38.1)	504 (39.0)	ns
Anxiety, no. (%)	79 (12.5)	235 (18.2)	*0.002*
Delusions, no. (%)	110 (17.4)	251 (19.4)	ns

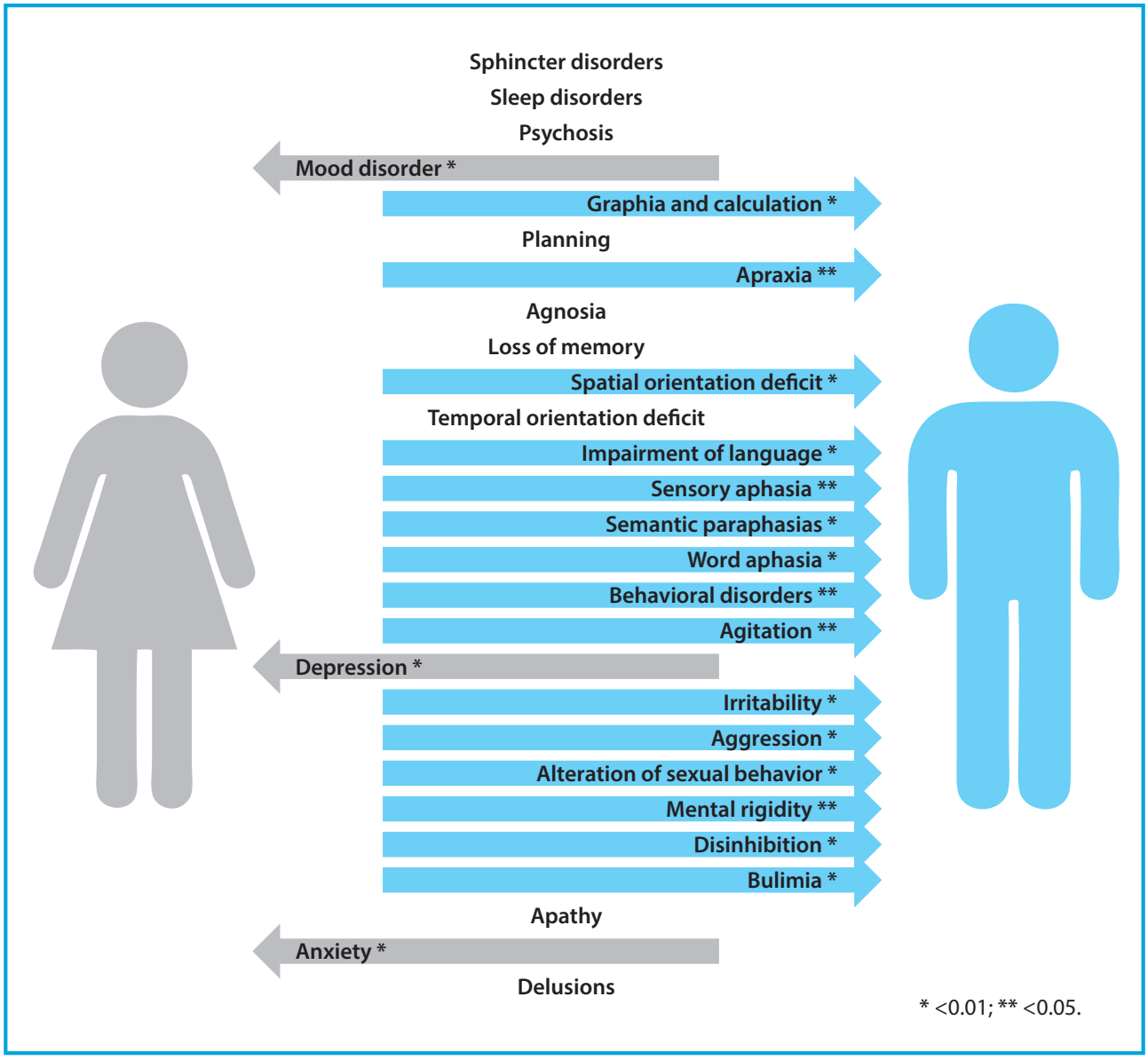

Figure 2. Arrows indicate which symptoms are statistically significant for men or women.

women and men respectively; p = 0.001) (Table 2). Considering the whole sample, we found a significant difference in the MMSE score of patients who were present in the first period (1996-2005) and those who took part in the second period (2006-2016), respectively 14.0 ± 7.0 and 16.9 ± 5.7 (p = 0.000) (Table 3).

Alcohol abuse was prevalent in men (p = 0.000) while women presented a larger number of risk factors: dystyroidism (p = 0.000), cholesterol (p = 0.001), hypertension (p = 0.000) and psychiatric disturbances (depression) (p = 0.000) (Table 4). No differences related to sex were observed according to APOEε4+.

From the evaluation of cognitive-behavioral clusters it emerges that men registered a significant prevalence in language impairment [46.6%, p = 0.000, specifically with sensory aphasia (p = 0.028), semantic paraphasias (p = 0.01) and word aphasia (p = 0.005)]; apraxia (37.5%, p = 0.035); spatial orientation deficit (62.7%, p = 0.006); agraphia and calculation problems (18.2%, p = 0.009) (Table 5) completed the picture.

In addition, behavioral disorders were more prevalent in men (62.6%, p = 0.012) and specifically bulimia (p = 0.000), disinhibition (p = 0.01), mental rigidity (p = 0.041), alteration of sexual behavior (p = 0.000), aggression (p = 0.000), irritability (p = 0.000) and agitation (p = 0.041), while women presented with mood disorder domain (41.9%, p = 0.000) and specifically depression (p = 0.000). These results are reported in Table 5, and shown in Figure 2.

Discussion

The main aim of this study was to analyze gender differences in a numerically relevant group of patients affected by AD diagnosed from 1996 to 2016 and followed at the RNC in southern Italy.

This was an observational study and data was retrospectively derived from clinical records, recorded by the same medical team using the same methods of observation and data collation.

Although the literature concerning gender differences in dementia is still scarce in the identification of specific features, the picture emerging from this work highlights significant differences.

Women with late onset AD represented about 2/3 of the whole group; this data is in agreement with previous data that reported a higher risk of developing dementia in women of a specific age[13-14].

We did not find differences in familial recurrence in the elapsing time between onset and the first consultation, follow-up, duration of the disease, ADL, IADL, APOEε4+.

In addition, follow-up (about 4 years) did not highlight substantial gender differences, suggesting that access to care was similar for both genders[15]. However, for both genders, the central element that emerges is the long time lapse (4 years) between the appearance of early symptoms and the first consultation. This time lapse diverges radically from national and European data, which varies between 36 and 63 weeks[16]. The critical point is the geographical and cultural setting of our sample. Belonging to a region of southern Italy where being affected by AD still represents a stigma, it reveals a culture of fear and marginalization of the disease that would require enormous effort to combat.

The positive trend in the elapsing time between onset of the disease and the first examination should however be stressed: it seems that in the latter period (2006-2016) people submitted to clinical observation about 6/8 months earlier in comparison with the previous decade. This data is probably consistent with the difference in MMSE score (14.0 ± 7.5 vs 16.9 ± 5.7).

The delay in diagnosis was related to the low cultural level (76.5% <5 years in our late onset patients) and women were less educated than men (20.4% completely illiterate and only 50.5% had at least 5 years of schooling). Correlation between low education level and AD confirms the higher probability of women of being exposed to the risk of dementia, as already reported[17]. On this subject, an epidemiological study on dementia in Europe and its impact over the last 20 years highlighted a reduction in the incidence of the disease due to the growing education level[18].

The strong correlation between dementia and cardio-cerebro-vascular factors (hypertension, diabetes and obesity[19-21]) is a well-known phenomenon, prevalent in women as well as in our sample where women are more affected by vascular and metabolic diseases. Only alcohol abuse is prevalent among male patients (7.4%). Other major differences related to the speed and degree of cognitive deterioration.

Women were more impaired at the first visit, although the duration of the disease was the same in male patients (15.9 ± 5.9 vs 17 ± 6.5). Cognitive impairment was moderate-severe with about 1 point less at MMSE than men as already evidenced by other authors[22] and suggesting a faster decline of women at the early stages of the disease. Four years from the onset, the decline was uniform and there were no gender differences. Although this trend complies with previous studies in the literature[23], the data lends itself to many interpretations that enable us to hypothesize new characterizing scenarios concerning the onset.

Signs of an ongoing brain disease tend to be recognized later in women, and are therefore not exactly dated, in a context where social and cultural dynamics reduce the perception of the disease, both by patient and family. The woman is probably able to disguise the progression of a disease such as Alzheimer's disease, because she continues to perform everyday tasks rather like an automated mechanism with the functions deeply rooted in her being. Making the bed, laying the table, cooking and taking care of family members, are almost atavistic tasks (in our country) learned during childhood and performed during the span of a lifetime. Signs of the disease, in women, are visible only when the decline is at a more advanced stage and "motoric rituals", previously carried out without any hitch, become very difficult due to apraxia or dysexecutive impairment. In contrast, men have greater exposure to social life and practical tasks. These factors make the signs of the disease visible at an earlier stage compared to women. Moreover, men are generally responsible for the economic administration of family life: the early impairment in calculation ($p = 0.009$) facilitates an earlier diagnosis.

Another characteristic blurring identification of the AD in women is the maintenance of good verbal fluency, while 50% of males exhibit speech problems. This is in agreement with literature data[24] and reinforces the hypothesis that highly-educated patients greatly deteriorate in language functions[25]. It turns out indeed, that the best preservation of language functions in women become a problem leading to a delay in diagnosis[26].

The impressive behavioural and psychiatric symptoms (BPSD) exhibited by males (disinhibition, aggressiveness, abnormal sexual behavior, bulimia, mental rigidity and irritability), already reported in the literature[27] led to an easier identification of the AD, while women's depression is "silent" and under recognized and this probably contributes to the late identification of the disease[28].

Thus, we can conclude that the AD phenotype is gender-related with some discrete characteristics: more mood disorders in women with a worse cognitive impairment, and a more rapid progression in men, accompanied by an aggressive behavioral disorder.

Why and on what basis do these differences occur?

Some possible fields such as different connexions, different hormonal background, different genetics (or different expression of genes), different load of risk factors, can be investigated for explanations.

Gender differences in behavioral and cognitive functioning are widely established in the current scientific literature. Biological and genetic differences in association with environment and culture have resulted in the cognitive and behavioral differences between men and women. The different hormonal background, among the biological factors, may play a pivotal role in mediating these differences in different brain connections as well. The brain must be considered as a large-scale network of interconnected nodes within the human connectome. Small world network models could be relevant for understanding the emergence of complex behaviors and the resilience of brain systems to pathological attack by diseases or aberrant development[29]. Gender differences in the brain connectome may provide an important foundation for delineating the pathophysiological mechanisms underlying sex differences in neuropsychiatric disorders. A study based on 949 youths using the diffusion-based structural connectome of the brain, established that male brains are optimized for intra-hemispheric communication and facilitate connectivity between perception and coordinated action whereas female brains, optimizing inter-hemispheric communication, facilitate communication between analytical and intuitive processing modes[30]. This happens in the physiological domain. When considering the AD related risk, Mosconi[31], studying Amyloid Positron emission Tomography (PET) and Fluorodeoxyglucose (FDG) PET, found a progressively increasing risk of AD in women undergoing menopausal changes. This suggests that endocrine aging accelerates chronologic aging in the female brain by several years, if not decades, prior to emergence of possible clinical symptoms of AD.

Gene expression profiles revealed substantial differences in the trajectory of aging changes between female and male brains. In female brains, 44.2% of genes change from 6 months to 9 months and 2/3 showed downregulation. In contrast, in male brains, this happens only in 5.4% of genes over the same period. This means that female and male brains follow profoundly different trajectories with age: the brains of women undergo age-related changes much earlier than male brains; these precocious changes in female brains signal the onset of a hypometabolic phenotype, at risk for AD. These findings provide a mechanistic rationale for female susceptibility to AD and suggest a potential window of opportunity for AD prevention and risk reduction in women[32]. Also sex-specific differences in neuro-mediators have been identified in male and female brains: they are neurochemically distinct in relation to dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA) systems with serotonin that sexually differentiate at multiple levels[33].

Conclusions

Behind the classic memory impairment and temporal disorientation, present in virtually all men and woman, a different AD phenotype between the two genders emerges from this work. These differences could originate from the profound cerebral differences (genetic, hormonal and in brain connections) that exist between the two sexes. More research work, however, is needed because results are still at the initial stage. All types of dementia have to be studied in this new light and verified in different contexts. Gender-specific treatment and care might assume a higher degree of importance.

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Key messages

- Gender perspective is needed to perform research in the field of dementia.
- Different dementia disorders have different expressions in the two sexes: biological and genetic differences in association with environment and culture have resulted in cognitive and behavioral differences among men and women.
- In our study, memory impairment and temporal disorientation, classical symptoms in Alzheimer's disease, are demonstrated in relation to all men and woman.
- Our female sample is poorly educated, with worse cognitive impairment and mood disorders.
- Men displayed a faster cognitive impairment and an aggressive behavioral picture.

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