

Investigation of Factors Affecting Apathy in Three Major Types of Dementia

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ABSTRACT

Introduction: Apathy is an important factor in the clinical management of dementia, as it has been associated with poor disease outcome, reduced daily functioning and caregiver distress. Considering apathy as a problem that needs to be managed and knowing the factors affecting apathy will enable appropriate initiatives to be planned. This study was conducted to compare apathy across three types of dementia and determine the factors affecting apathy for each of the three types of dementia.

Methods: The sample consisted of 46 patients with Alzheimer's disease (AD), 31 patients with frontotemporal dementia (FTD) and 29 patients with vascular dementia (VaD). Apathy was assessed using the Neuropsychiatric Inventory-apathy subscale (NPI), dementia severity was assessed using the Clinical Dementia Rating Scale (CDR), cognitive status was assessed using the Mini Mental Status Examination (MMSE) functional ability was measured with the Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton-Brody Instrumental Activities of Daily Living (IADL). This is a descriptive and cross-sectional study.

Results: Significant differences were found between the apathy score of three types of dementia. Cognitive impairment correlated significantly with the apathy score in AD and VaD. Functionality scores and severity of dementia showed a significant correlation with apathy in each group. No statistically significant relationship was detected between age, gender and apathy. Multiple regression analyses show that apathy scores correlated with IADL in patients with AD.

Conclusion: This study demonstrated that apathy is very common symptom in patients with FTD as well as patients with AD and VaD. Health professionals need to be aware of recognize apathy. Patients should be assessed for apathy regardless of dementia types, age and gender.

Keywords: Apathy, neuropsychiatric symptoms, Alzheimer's disease, frontotemporal dementia, vascular dementia

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INTRODUCTION

Neuropsychiatric symptoms are experienced over the course of the disease by people with dementia. In this regard, acquiring insight into neuropsychiatric symptoms is important for dealing with patients with dementia. Apathy is common neuropsychiatric symptoms and is defined as a decline in goal-directed behavior, decreased emotional response and lack of motivation (1). The frequency and severity of apathy differ according to types of dementia. The prevalence of apathy in frontotemporal dementia (FTD) ranges from 62 to 100% (2–3) from 24.0 to 95.5% in Alzheimer's disease (AD) (1–6) and from 30.9 to 65.40% in vascular dementia (VaD) (6–8).

In addition to its high prevalence, apathetic behavior is an important factor in the clinical management of dementia. The clinical significance of apathy arises from the fact that it causes a faster deterioration of cognitive and functional abilities and this creates much more work for the caregivers (9). In the literature, there are studies reporting that, it has been associated with poor disease outcome, reduced daily functioning, social isolation, caregiver distress and burden (10–12). One of the major findings

of Moretti et al.(13) was that apathy is badly tolerated and experienced by caregivers as a dramatic even and as even worse than memory loss or verbal defect. People with apathy are able to perform basic activities of daily living less than their cognitive status allow (13). Therefore, it affects the quality of life both the patients and their caregivers, as evidenced by its association with an increased likelihood of institutionalization (14). However, apathy is a neglected symptom, and in some communities is not considered as a symptom at all, but rather as an indolent or idle attitude. Sometimes it is not considered an inevitable consequence of the disease, and causes the patients to be labeled as "stable/lazy" by both formal and informal caregivers. Because of this, some families giving care do not take patients who are family members to doctors as early as they should (15). Considering apathy as a problem that needs to be managed and knowing the factors affecting apathy will enable appropriate initiatives to be planned. A better understanding of the associated risk factors is necessary for the development of appropriate interventions for apathy (16). For better understanding about factor affecting apathy according to dementia types more studies are needed. Few studies in the literature

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have compared factors affecting apathy in AD, FTD and VaD. The aim of this study was to compare apathy across three types of dementia, which are commonest dementia types and determine the factors affecting apathy for each of the three types of dementia.

METHODS

Design and sample

A comparative descriptive study design was used. The sample selection was carried out using nonprobability convenience sampling. Participants were 46 with AD, 31 with FTD and 29 with VaD, a total of 106 people with dementia who attended the outpatient neurology department between January and June 2016. Three subtypes of FTD; behavioral variant FTD (bvFTD; n=17), semantic variant of primary progressive aphasia (n=8), non-fluent variants of primary progressive aphasia (n=6) and two subtypes of VaD; subcortical VaD (n=21), cortical VaD (n=8) were included in the sample. We used DSM-IV for the dementia diagnosis, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) criteria for diagnosing AD, National Institute of Neurological Disorders and Stroke-Association International pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for diagnosing VaD, and Rascovsky et al.'s criteria for FTD. Participants with 4 and more than points on the NPI apathy subscale considered as apathetic. Subjects were excluded if they had been using antipsychotics during the one month prior to assessment and if there was no primary caregiver. In addition, those with more than 18 points on the Cornell Scale for Depression in Dementia (CSDD), a score which indicates a definite major depressive episode, were also excluded.

Dementia groups were compared in terms of factors that may affect the apathy score. Groups were similar in terms of education ($p=0.14$), marital status ($p=0.40$) and mini mental state examination scores (MMSE) ($p=0.20$). Comparison of the the neuropsychiatric inventory (NPI) scores of the three groups revealed that there were no statistically significant differences between groups ($p=0.07$). The age of the patients ($p=0.01$), gender ($p=0.01$), clinical dementia rating (CDR) ($p=0.00$), duration of illness ($p=0.00$) and Katz Index of Independence in Activities of Daily Living (ADL)/Lawton-Brody Instrumental Activities of Daily Living (IADL) ($p=0.02$, $p=0.04$) scores were not similar in each group. ANOVAs co-varied for age, stage of dementia, duration of illness and functional scores were performed to compare apathy scores in each dementia group.

Data collection and ethical consideration

This study was conducted in the outpatient neurology department of Dokuz Eylul University Hospital. The cognitive function (MMSE) and stage of dementia (CDR) evaluated by a neurologist researcher (GY). Functional tests (ADL and IADL) and neuropsychiatric test evaluated by a nurse researcher (MAA). For CDR, ADL, IADL and NPI interviewed with primary caregivers. The primary caregivers were a family member (spouse, sister, brother, daughter, son) of the patients. The study was consonant with the World Medical Association Declaration of Helsinki. Additionally, it was approved by the Ethical Committee for the Noninvasive Research Ethics Board of Dokuz Eylul University (Ethical Consideration Number: 2016/02-34). Participants were informed about the study and if they agreed to take part in the study, their written permission was received.

Instruments

A demographic Characteristics Questionnaire was administered. Apathy was assessed using the Neuropsychiatric Inventory-aphathy subscale (NPI-aphathy subscale) which is commonly used instruments in research on apathy in dementia (17, 18). NPI apathy subscale scores range from 0 to 12. Higher scores indicate more severe apathy and a cut-off score of

4.0. The frequency and severity of 12 specific behavioral and psychiatric symptoms of dementia are rated on the NPI. The total scores of the NPI range from 0 to 144, with higher scores indicates greater behavioral symptoms.

Dementia severity was assessed using the CDR. It rates according to the degree of cognitive loss. CDR 0 means that no dementia, 0.5 mild cognitive impairment, 1 mild dementia, 2 moderate dementia, 3 severe dementia. In this study we excluded CDR-0.5 which mostly indicates mild cognitive impairment (19). Cognitive status was assessed using the MMSE (range 0–30) in which a higher score shows better cognitive functioning. Functional ability was measured with ADL. Daily living activities are fundamentals for self-care and independence. The scores of the ADL range from 6–18. A score of 13–18 indicates full function, 7–12 indicates moderate impairment and 6 indicates severe functional impairment. IADL are activities essential for independent living. The scores of the IADL range from 8–24. A score of 17–24 indicates full function, 9–16 indicates moderate impairment and 8 indicates severe functional impairment.

Statistical analysis

Nonparametric statistics were used for discrete variables. The Statistical Package for the Social Sciences version 22.0 (SPSS Armonk, NY: IBM Corp) was carried out for statistical analysis. A value of $p<0.05$ (95% confidence interval) was considered statistically significant. The mean age of the patients, years of education, duration of illness, MMSE, NPI, ADL and IADL mean scores by groups were analyzed using the Kruskal-Wallis test. Patients' marital status, gender and CDR in the groups were analyzed by a chi-square test (Table 1). Analysis of covariance was used to control the confounding factors (age, duration of illness, ADL, IADL, CDR). Multivariate logistic regression analysis was used to assess which factors predict apathy in different types of dementia. Independent variables removed from the model by VIF were higher than 10 and tolerance was less than 0.20. The significance level was accepted as 0.05.

RESULTS

Occurrence and apathy score

In the present study, the occurrence rate of apathy was 66.7% in patients with FTD (N=31), 55.2% in VaD (N=29) and 50.0% in AD (N=46) groups. There were no significant differences among the groups ($\chi^2=2.446$, $p=0.29$). The average scores for apathy were, respectively, 6.227 ± 0.809 , 6.197 ± 0.787 and 4.136 ± 0.613 . The scores for apathy in FTD and VaD were found to be significantly higher than for those in the patients with AD, controlling for disease severity as shown by the CDR score, age, duration of illness and functioning levels ($F=3.191$, $p=0.04$).

Relationships of demographic and clinical characteristics to apathy scores within groups

The correlation of demographic and clinical characteristics and apathy score within each group are shown in Table 2. The MMSE scores correlated significantly with the apathy score in AD ($r=-0.410$) and VaD ($r=-0.537$) groups ($p=0.00$). There were no significant correlation between the apathy score and MMSE score in FTD. Additionally, CDR, ADL, IADL scores correlated significantly with the apathy score between the three groups (Table 2).

Multivariate logistic analysis

The correlation analysis was done between demographic and clinical variables and apathy and significant variables were included in the model. Analysis indicated that MMSE, CDR, ADL, IADL predicted a significant apathy score in the groups. For AD, $R=0.688$, $R^2=0.474$, $F=9.222$, $p=0.000$. These variables explained 47.4% of total variance of apathy score. A specific variable contributing to apathy score was IADL ($\beta=-0.491$). For

Table 1. Demographic and clinical characteristics of patients

	AD X ± SD (N=46)	FTD X ± SD (N=31)	VaD X ± SD (N=29)	χ ² kw	p
Age	73.83±10.28	68.13±9.52	74.17±10.49	7.912	0.01*
Education	7.72±4.85	9.55±4.43	7.69±4.40	3.905	0.14
Duration of diagnosis	4.13±2.81	5.41±2.74	3.31±2.81	10.537	0.00*
MMSE	16.17±8.60	13.03±11.17	18.07±8.44	3.179	0.20
NPI	32.33±15.80	30.27±16.62	21.66±12.78	5.171	0.07
ADL	14.30±3.92	11.81±4.72	14.93±2.86	7.231	0.02*
IADL	13.91±5.95	11.90±5.87	14.97±5.30	6.190	0.04*
Gender	% /n	% /n	% /n	χ²	p
Female	56.5% /26	51.6% /16	24.1% /7	8.361 ^a	0.01*
Male	43.5% /20	48.4% /15	75.9% /22		
Marital Status					
Married	69.6% /32	77.4% /24	82.8% /24	1.789 ^a	0.40
Single	30.4% /14	22.6% /7	17.2% /5		
CDR					
1	65.2% /30	38.7% /12	75.9% /22	21.523 ^a	0.00*
2	26.1% /12	16.1% /5	20.7% /6		
3	8.7% /4	45.2% /14	3.4% /1		

^aYates correction.

*p<0.05

MMSE, mini mental state examination; NPI, neuropsychiatric inventory; ADL, Katz index of independence in activities of daily living; IADL, Lawton-Brody instrumental activities of daily living; CDR, clinical dementia rating scale.

Table 2. Correlation of demographic and clinical characteristics and apathy scores

	AD		FTD		VaD	
	r	p	r	p	r	p
Age	0.233	0.12	-0.273	0.13	0.091	0.64
Gender	-0.120	0.42	-0.142	0.44	0.046	0.81
MMSE	-0.410	0.00*	-0.313	0.08	-0.537	0.00*
CDR	0.452	0.00*	0.461	0.00*	0.424	0.02*
ADL	-0.623	0.00*	-0.351	0.05*	-0.482	0.00*
IADL	-0.637	0.00*	-0.387	0.03*	-0.555	0.00*

*p<0.05

MMSE, mini mental state examination; NPI, neuropsychiatric inventory; ADL, Katz index of independence in activities of daily living; IADL, Lawton-Brody instrumental activities of daily living; CDR, clinical dementia rating scale.

FTD, $R=0.541$, $R^2=0.292$, $F=2.683$, $p=0.049$. These variables explained 29.2% of total variance of apathy score. For VaD, $R=0.639$, $R^2=0.408$, $F=4.140$, $p=0.011$. These variables explained 40.8% of total variance of the apathy score (Table 3).

DISCUSSION

In agreement with previous studies, this study revealed that apathy was a frequent symptom in all dementia groups, and that the apathy score was especially high in the FTD and VaD groups. Prior studies have generally investigated apathy without regard to the type of dementia. Previous studies making comparisons according to dementia types have been carried out between AD and FTD patients' groups (1, 2) or AD and VaD patients' groups, (6, 20). The present study compared the apathy profile among people with AD, FTD and VaD, and determined the factors affecting apathy.

In the present study, the scores of apathy in FTD and VaD were shown to be significantly higher than those in the patients with AD ($F=3.167$, $p=0.046$). Apathy was more prevalent and severe in FTD than AD and this in agreement with previous reports (1, 3). Higher levels of apathy have been reported FTD (1, 3) especially bvFTD (12) than in AD. Possible mechanisms related to a tendency for higher apathy scores in FTD could be due to the wider pathological involvement of the orbitofrontal cortex and medial frontal regions that are part of the attentional/motivational network (21). In the literature, there are studies reporting that symptoms of apathy were both more prevalent and severe in VaD (3, 22) especially subcortical VaD (7, 8) compared with AD. It stated that apathy is a primary consequence of subcortical VaD (23) and it may evolve rapidly in subcortical VaD compared with AD (8). Our vascular dementia group more consisted of subjects in subcortical vascular dementia and in the early stages of dementia. The VaD group reflects the involvement of the subcortical-frontal pathway, which is a hallmark of frontal-subcortical

Table 3. Multivariate logistic regression analysis using NPI-apathy scores from FTD patients

		B	Std. Error	Beta	t	p	(95% CI)
AD	MMSE	0.025	0.099	0.046	0.248	0.805	-0.167–0.210
	CDR	2.171	1.248	0.306	1.741	0.089	0.837–5.553
	ADL	-0.038	0.230	-0.032	-0.167	0.869	-0.390–0.520
	IADL	-0.382	0.137	-0.491	-2.793	0.008*	-0.604–0.058
	Constant	6.114	4.050		1.510	0.139	-5.291–10.845
FTD	MMSE	0.083	0.165	0.170	0.504	0.618	-0.257–0.302
	CDR	2.832	2.058	0.480	1.376	0.181	-1.396–5.517
	ADL	0.135	0.301	0.116	0.449	0.657	-0.487–0.554
	IADL	-0.386	0.234	-0.411	-1.648	0.111	-0.792–0.072
	Constant	4.005	7.180		0.558	0.582	-3.996–18.950
VaD	MMSE	-0.052	0.130	-0.084	-0.397	0.695	-0.331–0.190
	CDR	0.437	2.073	0.044	0.211	0.835	-2.879–4.291
	ADL	-0.514	0.410	-0.283	-1.252	0.233	-1.344–0.338
	IADL	-0.315	0.226	-0.322	-1.397	0.175	-0.730–0.186
	Constant	17.806	7.090		2.511	0.019	3.163–31.078

*p<0.05

AD (R=0.688, R²=0.474, F=9.222, p=0.000)FTD (R=0.541, R²=0.292, F=2.683, p=0.049)VaD (R=0.639, R²=0.408, F=4.140, p=0.011)

MMSE, mini mental state examination; NPI, neuropsychiatric inventory; ADL, Katz index of independence in activities of daily living; IADL, Lawton-Brody instrumental activities of daily living; CDR, clinical dementia rating scale; 95% CI, 95% confidence intervals.

circuit dysfunction in apathy, that occurs with cerebrovascular disease (7, 22). Changes mostly occur in the posterior cortical region in people with Alzheimer's disease. It is thought that this region does not play a primary role in the development of symptoms such as apathy (23).

Factors affecting apathy score

The results of this study revealed that apathy was not only common in people with dementia, but also it was correlated with loss of cognitive ability, increasing dementia severity and the functional decline (Table 2).

Similarly to previous studies, apathy shows a negative correlation with MMSE in AD and VaD groups. Likewise other studies have showed that the apathy score correlates with cognitive impairment in people with AD (11, 24) and VaD (20). However, apathy did not show a correlation with MMSE in FTD. It has been pointed out that the relationship of cognitive changes seen in VaD with MMSE is more similar to people with AD than to people with FTD (3). This similarity is thought to explain why MMSE and apathy scores were found to be correlated in both dementia types. FTD exhibits a cognitive neuropsychiatric profile characterized by executive dysfunction (25). It is believed that there was no correlation because changes in FTD could not be determined by a global cognitive measurement tool such as MMSE. Decreasing cognitive function leads to negative outcomes for patients and caregivers. It causes deficits in daily functioning and increasing caregiver burden (26). So that apathy causes decrease in cognition it is important to detect early would allow appropriate intervention.

Likewise, in other studies apathy correlates with CDR in people with AD (11), FTD and VaD (27). Apathy increase as the disease progressed (27). Apathy has been attributed to disruption of frontosubcortical circuits involving the basal ganglia, thalamus, and frontal lobes regardless of dementia type. Apathy correlates with increased neuropathological markers and atrophy in frontal region in degenerative dementias such as AD and FTD, and cortical lesions in the frontal region in people with VaD

(22, 28). Subcortical VaD disturbs corticosubcortical circuits with lacunar lesions and white matter ischaemic injury. Cortical lesions in VaD likewise commonly involve frontal regions and may disrupt corticosubcortical circuits mediating motivational behavior (28). As dementia progresses through stages, the severity of apathy increases due to decreased number of neurons in these regions. Apathy is seen any stage and types of dementia but it should be considered that it would be more prevalent and severe as the disease progressed.

Similarly to other studies, this study reported that apathy correlates with functional decline in AD (4, 11, 20), FTD (1, 12) and VaD (20). There is a vicious cycle between apathy and deterioration in functionality. There are studies showing that functional reduction is a risk factor for apathy and that apathetic people become also less functional over time (4). Merrilees et al. (12) found that apathy was associated with lower levels of mobility. People with apathy are able to perform basic activities of daily living less than their cognitive status allow (13). A specific variable contributing to apathy score in AD was IADL ($\beta=-0.491$). IADL, which requires the use of both cognitive and motor functions, exhibits performance in more complex activities compared to ADL. Boyle et al. (29) found that apathy accounted for 27% of the variance in IADL, whereas it accounted for 15% of the variance in ADL in AD. In the Baltimore ECA study (30) as a result of 1-year follow-up of older adults, the risk of disability in IADL was initially found to be 4.39 times greater in those who were apathetic compared to those who were not. This risk was found to be 2.88 for ADL. Boyle and the Baltimore ECA results support the results obtained from this study. It was suggested that apathy decreases functionality, increases the risk of disability. Functional disability cause caregiver distress and burden (20). In this sight, it is important to detect early would allow appropriate intervention.

This study found that apathy did not correlate with age and gender in people with AD, FTD and VaD (Table 3). No studies are to be found in the literature investigating the correlation between apathy and age in people

with FTD and VaD. Study results examining the correlation between apathy and age in people with AD are different. Similar to earlier studies, our study indicates that apathy is not correlated with age in people with AD (5). In contrast to these studies, Starkstein et al. (4) found that apathy positively correlated with age in people with AD. Their study pointed out that the reason why apathy progresses as the patient gets older may be because age has a correlation with decreased social interaction. Honda et al. (15) results support the hypothesis that apathy is involved in social withdrawal. Since in Turkish society, most older adults live with their families (31) social interaction continues, and it is thought that the correlation was not found in our study due to this.

Most of the previous studies show that there is not a statistically significant relationship between gender and apathy, and it affects males and females equally (5, 11). It has been indicated that pathologies in the orbitofrontal region is correlated with apathy in people with dementia (32). In a study conducted by Ballmaier et al. (33) on people with dementia, it was found that there was no statistically significant relationship between changes in the orbitofrontal cortex and gender. It is thought that there was no relation between apathy and gender since changes in apathy related to brain regions are similar in both males and females. People with dementia should be evaluated for apathy regardless of gender and age.

Findings of current study require confirmation from independent studies with a larger series of subjects because of the relatively small sample of AD, FTD and VaD patients taken into account in the present study. It is suggested that more detailed neuropsychological tests be used and quantitative data related to imaging should be included in future research.

CONCLUSION

This study demonstrated that apathy is common in patients with FTD as well as patients with AD and VaD. The current study also demonstrated that patients with FTD and VaD report more severe apathy than patients with AD. It was determined that apathy was correlated with cognitive impairments in the AD and VaD groups, and additionally correlated with functional dysfunction and dementia severity across all three types of dementia. Apathy may be seen a significant predictor of accelerated cognitive and functional decline. Intervening to reduce apathy may have a positive impact to patient and caregiver. Apathy should not be overlooked especially in cultures that have inclination for elderly not to motivate for their functional independence. Health professionals need to be aware of recognize apathy. Patients should be assessed for apathy regardless of dementia types, age and gender. The determination of the occurrence of apathy and factors affecting it will contribute to the planning of interventions to address this issue. It will be important to conduct interventional, prospective and culturally adapted studies for decreasing apathy in people with dementia.

Ethics Committee Approval: The study was consonant with the World Medical Association Declaration of Helsinki. Additionally it was approved by the Ethical Committee for the Noninvasive Research Ethics Board of Dokuz Eylul University (Ethical Consideration Number: 2016/02-34).

Informed Consent: Participants were informed about the study and if they agreed to take part in the study, their written permission was received.

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