Is anticholinergic use in elderly a risk factor for frailty?

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Running Head:**:Anticholinergic drugs effects on frailty**

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Abstract:

Aims of study: Frailty among the elderly refers to those with limited daily activity secondary to their physical, mental, psychological and/or social limits, in addition to comorbid diseases. The risks of disability, disease, hospital admission and death are higher in the frail elderly population . The prevalence of frailty has been found to be 4–16% in those aged 65 years or more. The use of drugs with anticholinergic burden (ACB) may lead to both unexpected adverse effects and an increased risk of frailty.

In this study, we evaluated the effect of anticholinergic burden on frail patients admitted to the geriatric outpatient clinic.

Materials and Method: Included in this prospective study were 125 frail patients aged 65 and above who presented to geriatric outpatient clinics between March and November 2016. The Fried Criteria were applied for the diagnosis of frailty in patients, with five clinical properties were assessed individually in each patient. Patients meeting 3 or more of the criteria were accepted as frail. The Anticholinergic Cognitive Burden Scale was used to calculate the anticholinergic burden score for each patient. The total ACB score is calculated by summing the score for each drug. Anticholinergic effect was accepted as “none” when the total value was 0, and “present” when the total value was 1 and above.

Result: A total of 125 elderly frail patients were included in the study, with a mean age of 76.74±6.67 years. The patients were composed of 77 (61.6%) women and 48 (38.4%) men. The effect of ACB was evaluated in the frail patients. In the frail patient group, 71 patients (56.8%) used no drugs with ACB, while 54 patients (43.2%) had a history of using drugs with ACB. Patients in the two frail group were evaluated based on the presence of anticholinergic burden. The mean walking speed was found to be significantly different in the two groups ($p<0.001$). The weight of the patients in ACB present and none groups were compared with a t-test, and the difference between them was found to be significant ($p<0.05$), and weight loss was found to be greater in patients with ACB present group.

Conclusion:Use of drugs with an anticholinergic burden may be a risk factor for frailty by decreasing walking speed. Decreases in daily living activities and instrumental daily living activities were identified in frail patients using drugs with a high anticholinergic burden.

Keywords:anticholinergic burden, frailty, elderly

Introduction

Frailty is a state of weakness related to decreased physiologic reserves of the neurological, inflammatory, endocrinological, neuromuscular, metabolic and immune systems and organs with advancing age, and is accepted as one of the geriatric syndromes. (1) Frailty among the elderly refers to those with limited daily activity secondary to their physical, mental, psychological and/or social limits, in addition to comorbid diseases. (2) The risks of disability, disease, hospital admission and death are higher in the frail elderly population (3). The prevalence of frailty has been found to be 4–16% in those aged 65 years or more. (4,5) The use of drugs with anticholinergic burden (ACB) may lead to both unexpected adverse effects and an increased risk of frailty.

The number of drugs used as a person ages is increased due to physiological changes and comorbidities. Among the elderly population (aged ≥65 years), 23% of women have been shown to use ≥5 drugs, while this figure increases to 35–40% in those aged 75–85 years (6,7). Drugs are effective for the treatment of disease, but at the cost of side effects, and the risk of drug use with ACB effects is increased with an increased number of drugs. Almost 48% of elderly in the general population use drugs with ACB effects (8). Drugs with anticholinergic effects are associated with many adverse effects, and so their use among the elderly should be approached with caution, however, this fact is generally overlooked. Anticholinergic drugs have both peripheral and central adverse effects, including dry mouth, nausea, vomiting, constipation, abdominal pain, loss of taste, anorexia and ophthalmological problems among the former; and dizziness, tingling, headache, lethargy, weakness, nervousness, numbness, irritability, narcosis, mental confusion, dyskinesia, syncope, speech disorders and insomnia among the latter (9,10). These drugs have also been associated with physical functional disorder, delirium and mental disorders in geriatric patients (8,10,11), although the magnitude of these effects are unknown, especially in frail elderly patients.

The present study investigates the effect of drugs with ACB on frailty in elderly patients presenting to geriatric outpatient clinics.

Materials and Methods

2.1. Study design

Included in this prospective study were 125 patients aged 65 and above who presented to geriatric outpatient clinics between March and November 2016. Ethics Board approval was obtained for the study from the Gulhane Military Medical Academy Ethics Board, on June 12, 2017 and with decision number of 301-16/1648-946. All participants provided written, informed consent for their participation in the study.

Study Inclusion Criteria:

1. Aged over 65 years
2. No dementia and a Mini-Mental State Exam (MMSE) score of >24
3. Able to communicate
4. Having given written consent for participation in the study.

Study Exclusion Criteria

1. Those diagnosed with dementia at first presentation.
2. Immobile patients
3. Those diagnosed with a type of malignancy,
4. Those diagnosed with delirium,
5. Those who had undergone major surgery within the past 6 months
6. Those who experienced cardiac or cerebrovascular events during follow-up
7. Those with a history of lower extremity fracture that prohibited walking
8. Those with an infectious disease
9. Those who declined to sign the informed consent form, or withdrew their consent.

2.2. Diagnosis of frailty:

The Fried Criteria were applied for the diagnosis of frailty in patients (12), with five clinical properties were assessed individually in each patient. Patients meeting 3 or more of the criteria were accepted as frail.

1-Weight loss: Undesired weight loss of ≥4.5kg or ≥5% body weight over the past one year.

2-Weakness: The height and weight of the participants was measured at the outpatient clinics and the Body Mass Index (BMI) (kg/m^2) was calculated. Handgrip strength was measured twice using a Jamar manual dynamometer (Jamar hydraulic

hand dynamometer [Patterson Medical Ltd, Warrenville, IL, USA]), and the mean of the two values was used. Handgrip strength according to BMI was evaluated.

MEN	
BMI (kg/m^2)	Handgrip strength (kg)
≤24	≤29
24.1–28	≤30
>28	≤32
WOMEN	
≤23	≤17
23.1–26	17.3
26.1–29	≤18
>29	≤21

BMI: Body mass index

3-Fatigue or debility were evaluated based on the Center for Epidemiologic Studies Depression Scale (CES-D). The participants were asked the question "How many times in the past week have you felt like this?", and the responses were grouped as rarely or none (<1 day), few or very few times (1–2 days), half the time (3–4 days), and most of the time. Those who responded with "half the time" or "most of the time" were accepted as frail for the debility criterion.

4-**Walking Speed** was measured in seconds over a 4.5–meter walking track. Participants were accepted as positive based on scores of 7 seconds in men measuring ≤173 cm in height, and 6 seconds in men measuring >173 cm; and 7 seconds in women measuring ≤159 cm in height, and 6 seconds in women measuring >159 cm for frailty.

5-Level of physical activity The daily activities of the patients were not assessed, with only activities carried out as exercise being considered. Scores of <383 kcal in men and <270 kcal in women were accepted as positive.

Patients meeting three or more of the above were accepted as frail.

2.3 Anticholinergic Drugs

Information about medication use was collected during the clinic visit, with the anticholinergic burden of the patients calculated from the list of medications they used regularly at the time of inclusion in the study. Only the drugs that were used regularly were entered in the calculation. The Anticholinergic Cognitive Burden Scale was used to calculate the anticholinergic burden score for each patient (13)**.** The anticholinergic scores of all drugs were summed. Anticholinergic effect was accepted as "none" when the total value was 0, and "present" when the total value was 1 and above**.** Topical and ophthalmic drugs, drugs for the auditory canal and inhalation drugs were not included in the scoring. Drugs used only when necessary were not included (most commonly, pain killers)

2.4 The daily living activities of the patients were also evaluated.

Daily living activities and instrumental living activities were compared between the ACB score none and present groups. The Barthel Index for Activities of Daily Living (ADL) scale and the Lawton and Brody's Instrumental Activities of Daily Living (IADL) scale were applied for the measurement of daily living activities and instrumental daily living activities, respectively. The ADL and IADL tests of the patients with an ACB were found to be significant ($p<0.05$). (**Table 3**). The ADL an IADL score were lower in ACB present group than none group

Statistical analysis

The IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.) package program was used for the analysis of the data. Continuous variables were presented as mean±standard deviation (SD), and categorical variables as frequencies and percentages. The normality of the continuous variables was evaluated with a Kolmogorov-Smirnov test; differences between quantitative variables were analyzed with a Student's t-test, and, for variables with a non-normal distribution, a Mann–Whitney U test. The differences between groups of categorical variables were evaluated with a Chi-square test. P values of <0.05 were considered statistically significant.

The patents in the frail group were evaluated as ACB present or absent. The differences between the groups were evaluated with a Mann-Whitney test after a non-normal distribution was identified from the Kolmogorov-Smirnov test.

Weight loss values were compared with a t-test, and the difference between them was found to be significant (p=0.011603).

Results

A total of 125 elderly frail patients were included in the study, with a mean age of 76.74±6.67 years. The patients were composed of 77 (61.6%) women and 48 (38.4%) men. The effect of ACB was evaluated in the frail patients. In the frail patient group, 71 patients (56.8%) used no drugs with ACB, while 54 patients (43.2%) had a history of using drugs with ACB. The rate of ACB drug use in the present study was similar to that of other studies (14,15). The demographics of the patients are presented in **Table 1**.

Patients in the two frail group were evaluated based on the presence of anticholinergic burden. The mean walking speed was found to be significantly different in the two groups ($p<0.001$). The use of the ACB group of drugs may increase the risk of development of frailty (table 2).

Hand grip strength test was used to evaluate physical performance. The handgrip strength values were non-normally distributed. Muscle strength was assessed based on hand grip strength, measured using a dynamometer, for which two measurements of grip force (kg) were made with the dominant hand, and the mean score was calculated. In contrast to previous studies, no difference was found in the ACB and handgrip strength in frail patients in the present study **(Table 3**). Similarly, no association was found between ACB present and none groups on grip strength in the study by Juliette O'Connell (16), which may be attributable to the fact that the patients were unfamiliar with the handgrip measuring device.

The weight of the patients in ACB present and none groups were compared with a t-test, and the difference between them was found to be significant ($p<0.05$), and weight loss was found to be greater in patients with ACB present group (Table 2). Anticholinergic side effects can lead to weight loss by inhibiting food intake and appetite (17)**.**

Fatigue was found to be more common among the frail patients and higher among those with ACB, although the differences were not statistically significant.

An association was identified between anticholinergic drug and weight loss and walking speed, as two of the five items used for the diagnosis of frailty. ACB use can thus be considered as playing a significant role in the development of frailty.

Discussion

Functionality is decreased in frail patients, and anticholinergic drug use decreases functionality even further (10).

Drug use is generally more common among elderly patients with a high number of comorbidities, and the prescribed drugs generally have anticholinergic adverse effects. Inappropriate medication use is common among the elderly, and the use of medications with anticholinergic effects is associated with functional impairment in the elderly. The most commonly used drug groups with anticholinergic effects are for urinary incontinence and cardiovascular system, along with anti-hypertensive drugs, antihistamines and anti-Parkinson drugs. Some 51% of the general population is estimated to use anticholinergic drugs (11), and almost half of the elderly adults in society have a clinically significant anticholinergic burden.

The number of drugs used is increased in the elderly due to chronic diseases, and the possibility of the use of drugs with anticholinergic effects is high in this group of patients. Antipsychotics, antihistamines and drugs used for the treatment of incontinence generally have a high anticholinergic burden (18), and this side effect is increased under the cumulative effect of several anticholinergic drugs.

Study Limitations: One of the limitations of this study is the low number of patients included in the study. The anticholinergic burden scores were calculated using only the Anticholinergic Burden Scale in the present study. No calculation of cumulative burden was made, nor was the possible anticholinergic burden of other drugs taken into account.
Frailty is associated with an increased risk of mortality and morbidity, including falls, disability and hospital stay. Frailty might be a result of advanced age, but may also be attributed to secondary causes (19,20).

Conclusion:

Use of drugs with an anticholinergic burden may be a risk factor for frailty by decreasing walking speed. Decreases in daily living activities and instrumental daily living activities were identified in frail patients using drugs with a high anticholinergic burden.

This suggests that the use of drugs with anticholinergic effects increased functional impairment in frail patients. Practical applications for prescriptions may be used in the elderly to overcome this effect.

Further studies are required to better explain the effects of anticholinergic drugs on frailty.

	Value SD*
Age (years)	76.74±6.67
sex (female/male) %	61.6/38.4
BMI (kg/m^2)	28.83∓5.52
FBG (mmol/L)	112.11∓29.08
Urea	39.42∓11.990
Creatinine	11.90∓0.26
Total Cholesterol	205.57∓41.23
Triglyceride	136.79∓55.57
HDL-C	54.75∓13.27
Aspartate aminotransferase (AST)	21.75∓7.47
Alanine aminotransferase ALT	19.21∓15.67
Lactate dehydrogenase (LDH)	197.03∓52.8
Alkaline phosphatase (ALP)	83.36∓31.40
Uric acid	7.28∓1.2
Total Protein	7.67∓6.5
Albumin	4.18∓0.34
Calcium	9.40∓0.69

Sodium	136.8∓16.74
Potassium	4.47∓0.40
Vit B12	513.14∓256.8
Folate	18.96∓9
Ferritin	68.68∓53
Thyroid stimulating hormone(TSH)	2.34∓2.52
Vitamin D	26.38∓14.37

Table 1. Demographics in the frail group

Table-2-Comparison of anticholinergic burden effect on frailty criteria

	ACB none n = 70	ACB present n = 54	p
Weight loss (kg)	1.59±3.02	1.56±3.28	0.68
Hang grip (kg)	14.09±5.21	12.87±5.47	0.22
Walking speed (second)	4.85±1.80	6.28±3.11	0.00
Exhaustion (yes/no)	18 (25.7%)	22 (40.7%)	0.68
Exercise	yes= 28 (39.4%) no= 43 (60.6%)	yes= 20 37.0% no= 34 63.0%	0.85

Table-3- Comparison of Neuropsychiatric scale with frail

	ACB		
	present	none	P
ADL	93.13+-9.54	96.87+-4.84	0.036
IADL	13.51+-4.27	15.43+-2.90	0.013
handgrip strength	68.91±13.34	75.44±14.67	0.58

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