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Anticholinergic drugs use and risk of hip fracture in geriatric patients

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Aim: Limited research exists regarding the effect of anticholinergic drugs on fracture in geriatric Japanese patients. The aim of the present study was to establish whether anticholinergic load affects hip fracture and to clarify the risk based on the Anticholinergic Risk Scale score among geriatric patients in a convalescent rehabilitation setting.

Methods: The present nested case–control study included consecutive geriatric patients admitted and discharged from the convalescent rehabilitation ward between 2010 and 2016. Participants were divided based on the presence or absence of hip fracture during hospitalization. Demographic data, laboratory data and the Functional Independence Measure were analyzed between groups. The primary outcome was the presence of hip fracture. Multiple logistic regression analysis was carried out to analyze the relationship between anticholinergic drug use and hip fracture.

Results: In total, 601 participants (210 men, 391 women; interquartile range 73–85 years) were included in the present study. Multiple logistic regression analysis of hip fracture, adjusting for confounding factors, showed that anticholinergic drug use was independently and positively correlated with hip fracture. In particular, an increase in the Anticholinergic Risk Scale score by 2 points correlates with a 2.86-fold greater risk for hip fracture, and an increase of ≥3 points results in a 4.21-fold greater risk, both being statistically significant results.

Conclusion: Increased anticholinergic load during hospitalization might be a predictor of increased hip fracture in geriatric patients. **Geriatr Gerontol Int 2018; ••: ••–••.**

Keywords: anticholinergic drug, anticholinergic risk scale, convalescent rehabilitation, geriatric patients, hip fracture.

Introduction

According to a survey carried out in 2016 by the Ministry of Health, Labor and Welfare, fracture in older adults accounts for 12.1% of the long-term care required, and the degree of care increases with age. Furthermore, in the West, the annual rate of falls among older adults at home is approximately 30%.[1] Among these individuals, the rate of fracture is 5–6%, and 1% of these account for hip fractures.[2] However, a similar survey carried out in Japan among individuals residing in nursing homes found that the corresponding rate was considerably high (8%).[3] In most cases of hip fractures, it is difficult to recover gait function for maintaining a standing position without undergoing surgery. It has been reported that the prefracture gait function is restored in approximately two-thirds of patients, and that the mortality rate after 1 year of restoration is 11%.[4]

Medications are a potentially modifiable risk factor for falls and fractures. A meta-analysis found that use of benzodiazepines, antipsychotics and antidepressants was consistently associated with risk of falls and fractures.[5] Some commonly used antidepressants and antipsychotics have a high degree of anticholinergic activity,[6] but there is limited evidence regarding the risk of fractures associated with anticholinergic drugs.[7,8] Anticholinergic drugs are frequently prescribed to older adults, and are used by 23% of community-dwelling older and 60% of those residing in nursing homes. In addition, two or more types of such drugs are used by 13% of community-dwelling older adults and 34% of those residing in nursing homes.[9] Other drugs, such as antidepressants, antipsychotics and antihistamines, have significant anticholinergic side-effects, but owing to their often non-selective nature, the use of anticholinergic drugs is associated with major side-effects. Peripheral side-effects include dry mouth, constipation, urinary retention and blurred vision; central side-effects mainly include sedation, confusion, cognitive impairment and delirium.[10–12]

In the case of anticholinergic drugs, the total anticholinergic load of the administered drug is considered important, as it serves as an index – the Anticholinergic Risk Scale (ARS) score; the ARS score of each anticholinergic drug based on its anticholinergic potency is already known.[13] Therefore, in the convalescent rehabilitation ward that is inhabited largely by older adults, attention should be given to the total anticholinergic load during the onset of adverse drug events. Although a previous report has shown the association between anticholinergic drugs and falls, only a few reports have shown the association between anticholinergic drugs and fracture, especially in Japan.[8] Therefore, the present study aimed to evaluate the strength of anticholinergic potency using the ARS score, and to clarify the association between ARS scores and incidences of fracture, as well as the risk of fracture according to each ARS score in Japanese older adults.

Methods

Study design and participants

A nested case–control study was carried out in 929 participants discharged from the convalescence rehabilitation ward at Hitachinaka General Hospital, Ibaraki, Japan, between July 2010 and March 2016. The inclusion criterion was age ≥65years. The exclusion criteria were age <65 years, patients receiving steroid therapy, a history of osteoporosis or fracture and patients with missing data. Participants were divided based on the presence or absence of hip fracture from admission to discharge to the "fracture group" and "non fracture group."

Table 1 Baseline of demographic characteristics and laboratory data

Characteristic	All patients (n = 601)	Fracture group (n = 68)	Non-fracture group (n = 533)	P-value
Age (years)	79 (73–85)	80.5 (73–86)	79 (73–89)	0.2640†
Sex, *n* (%)				0.8373‡
Male	210 (34.9)	23 (33.8)	187 (35.1)	
Female	391 (65.1)	45 (66.2)	346 (64.9)	
Length of stay (days)	67 (47–86)	72 (49.8–85)	66 (46.5–87)	0.8590†
Bodyweight at admission (kg)	50.7 (43.8–58.8)	47.8 (42.5–58.0)	51.1 (43.8–58.8)	0.1293†
Bodyweight at discharge (kg)	48.2 (41.9–55.9)	45.4 (39.7–52.4)	48.6 (42.2–56.2)	0.0281†
Change in bodyweight (kg)	−1.6 (−3.9–0)	−1.8 (−5.6–0.5)	−1.6 (−3.6–0)	0.6183†
Body mass index at admission (kg/m^2)	22.0 (19.2–24.6)	21.8 (18.8–23.9)	22.0 (19.2–24.7)	0.3123†
Body mass index at discharge (kg/m^2)	21.0 (18.5–23.4)	20.4 (17.1–22.7)	21.0 (18.7–23.5)	0.0686†
Primary diagnosis, *n* (%)				0.1361‡
Cerebral infraction	284 (47.3)	30 (44.1)	254 (47.7)	
Intracerebral hemorrhage	155 (25.8)	16 (23.5)	139 (26.1)	
Subarachnoid hemorrhage	45 (7.5)	4 (5.9)	41 (7.7)	
Parkinson's disease	17 (2.8)	3 (4.4)	14 (2.6)	
Epilepsy	10 (1.7)	3 (4.4)	7 (1.3)	
Disuse syndrome	37 (6.2)	4 (5.9)	33 (6.2)	
Others	53 (8.7)	8 (11.8)	45 (8.4)	
Comorbidities, *n* (%)				
Cardiac disease	157 (26.1)	16 (23.5)	141 (26.5)	0.6052‡
Diabetes mellitus	139 (23.1)	18 (26.5)	121 (22.7)	0.4876‡
Hypertension	390 (64.9)	45 (66.2)	345 (64.7)	0.8137‡
Fall, *n* (%)	108 (18.0)	15 (22.1)	93 (17.5)	0.3511‡
No. drugs at admission	2 (0–5)	2 (0–5)	2 (0–5)	0.9023†
No. drugs at discharge	5 (3–7)	6 (4–7)	5 (3–7)	0.3111†
Change in no. drugs	1 (0–4)	1 (0–5)	1 (0–4)	0.4872†
ARS at admission (points)	0.07 ± 0.3	0.1 ± 0.3	0.01 ± 0.3	0.1825†
ARS at discharge (points)	0.8 ± 1.4	1.9 ± 2.3	0.6 ± 1.2	<0.0001†
Change in ARS (points)	0.7 ± 1.3	1.8 ± 2.2	0.5 ± 1.1	<0.0001†
FIM at admission (points)				
Total	80 (59–100)	75 (57.5–99)	80 (59–100)	0.3326†
Motor	56 (39.5–69)	52 (35.3–65)	56 (40–69.5)	0.2342†
Cognitive	26 (17.5–31)	24 (18.3–31)	26 (17–32)	0.6779†
FIM at discharge (points)				
Total	104 (77–115)	99.5 (71.8–115)	105 (77–115)	0.3304†
Motor	75 (54–83)	71.5 (51.5–82.8)	76 (55–83)	0.2263†
Cognitive	29 (20–33)	28 (22–33)	29 (20–33)	0.8889†
FIM gain (points)				
Total	13 (5–24)	13 (4.3–25.8)	13 (5–23)	0.8698†
Motor	11 (4–21)	11 (4–23)	11 (4–21)	0.7209†
Cognitive	1 (0–4)	2 (0–4)	1 (0–4)	0.2006†
Clinical laboratory data				
TP (g/dL)	7.0 (6.6–7.4)	6.9 (6.6–7.3)	7.0 (6.6–7.4)	0.3721†
Alb (g/dL)	3.9 (3.5–4.2)	3.8 (3.3–4.0)	3.9 (3.6–4.2)	0.0436†
CRP (mg/dL)	0.2 (0.1–1.6)	0.4 (0.1–2.8)	0.2 (0.1–1.5)	0.2137†
GNRI at admission	93.9 (76.5–104.1)	93.9 (79.4–102.4)	93.9 (74.8–104.4)	0.6025†
GNRI at discharge	88.5 (78.6–97.5)	83.9 (72.7–92.8)	90.1 (79.5–98.4)	0.0104†
GNRI ≥92	256 (42.6)	18 (26.5)	208 (43.3)	0.0392‡
GNRI <92	345 (57.4)	50 (73.5)	325 (60.9)	

†Mann–Whitney *U*-test. ‡χ^2-test. Alb, albumin; ARS, Anticholinergic Risk Scale; CRP, C-reactive protein; FIM, Functional Independence Measure; GNRI, Geriatric Nutritional Risk Index; TP, total protein.

Investigation items

Data regarding the participants' basic information were collected from their medical records at admission and discharge, as appropriate. This included their age, sex, length of stay, bodyweight (BW), change in BW, body mass index, primary diagnosis, comorbidities, a history of falls, number of drugs prescribed, change in the number of drugs, the ARS score, change in the ARS score, Functional Independence Measure (FIM) and FIM gain. Change in the ARS score was calculated by subtracting the score from admission to discharge with reference to a previous report.[13] Laboratory data were also collected from medical records at admission and discharge, as appropriate. These included albumin (Alb), total protein, the Geriatric Nutritional Risk Index (GNRI)[14,15] and C-reactive protein levels. The GNRI, a nutritional risk index, was calculated from the serum Alb concentration and BW using the following equation: GNRI = (14.89 × Alb concentration [g/dL]) + (41.7 × [actual BW / ideal BW]). The weight and Alb had been measured at admission and discharge. The ideal BW was defined as a body mass index of 22.0 kg/m^2, rather than the Lorentz formula.[16,17] There is reportedly no difference in GNRI between the use of the Lorentz formula and body mass index of 22.0 kg/m^2 for ideal BW. We divided patients into two groups according to GNRI at discharge: low GNRI (<92), indicating moderate or severe nutritional risk, and high GNRI (≥92), indicating low or no nutritional risk.[18]

Table 2 Multiple logistic regression analysis for hip fracture

Variable	AOR	95% CI	*P*-value
Age	1.015	0.972–1.061	0.4946
Change in ARS	1.709	1.414–2.087	<0.0001
FIM-T gain	1.001	0.982–1.021	0.8908
Change in bodyweight	1.009	0.960–1.073	0.7364
Change in no. drugs	0.935	0.833–1.041	0.2219
Alb	0.715	0.379–1.386	0.6336
Falls (yes)	1.201	0.552–2.465	0.3143

Alb, albumin; AOR, adjusted odds ratio; ARS, Anticholinergic Risk Scale; CI, confidence interval; FIM-T, Functional Independence Measure-Total.

Assessment

The present study used FIM as activities of daily living measurement. The FIM score, which includes 13 lower-order items regarding motor function (FIM-M) and five lower-order items regarding cognitive function (FIM-C), is one of the most common measures of activities of daily living.[19] Each item is scored on a scale of 1 point (total assistance) to 7 points (complete independence). The FIM total (FIM-T) score therefore ranges from 18 to 126 points. FIM scores were assessed by the multidisciplinary rehabilitation team including a rehabilitation physician, registered dietitian, nurse, physical therapist, occupational therapist, speech language-hearing therapist, and pharmacist at admission and discharge. Based on clinical judgment, appropriate rehabilitation was offered to all participants, regardless of their FIM score or length of stay.

Outcome measure

The primary outcome was the presence of hip fracture during hospitalization.

Statistical analysis

All statistical analyses were carried out using JMP Pro (version 13; SAS Institute, Cary, NC, USA). Data with a normal distribution were described by mean ± standard deviation. If not normally distributed, data were described by median (interquartile range 25th–75th percentiles). A *P*-value <0.05 was considered statistically significant.

The Mann–Whitney *U*-test and χ^2-test were used to analyze the differences between groups. Spearman's rank correlation test was carried out to detect correlation coefficients between the factors. The McNemar test was used to compare the ARS score and anticholinergic drugs at admission and discharge. A multiple logistic regression analysis that included variables (age, change in BW, change in number of drugs, change in the ARS score, FIM-T gain, Alb, presence of falls) as covariates was carried out after univariate analysis to identify which factors were associated with the presence of hip fracture.

Ethics

The study was carried out in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Hitachinaka General Hospital and School of Pharmacy, Nihon University.

Results

Descriptive and univariate analyses

We enrolled 929 participants during the study period, but excluded 215 aged <65 years, 45 receiving steroid therapy, 54 with a history of osteoporosis or fracture and 14 with missing data. Accordingly, 601 participants with a median age of 79 years (interquartile range 73–85 years; 210 men) were included in the study. Table 1 shows the demographic characteristics by the presence (n = 68) and absence (n = 533) of hip fracture during hospitalization. Significant differences were BW at discharge, ARS at discharge, and change in the ARS score, Alb and GNRI at discharge.

Multiple logistic regression analysis for hip fracture

Table 2 shows the results of multiple logistic regression analysis of hip fracture after adjustment for confounding factors including age, change in BW, change in the number of drugs, change in the ARS score, FIM-T gain and Alb, and the presence of falls as independent factors associated with hip fracture. There was no strong internal correlation between the variables using Spearman's rank correlation test. A change in the ARS score (adjusted odds ratio 1.709, 95% confidence interval [CI] 1.414–2.087, $P \leq 0.0001$) was independently associated with the development of hip fracture.

Change in the ARS score during hospitalization

Participants receiving 0 points accounted for approximately 91% of the total population at admission, but this decreased significantly to 68.2% at discharge. In contrast, participants scoring 1, 2 and ≥3 points on the ARS increased from 5%, 1.5% and 2.5% at admission, respectively, to 13.1%, 6.2% and 12.5% at discharge, respectively (Fig. 1). Figure 2 provides a comparison of the anticholinergic drugs prescribed at admission and discharge. It was notable that chlorpromazine, hydroxyzine, olanzapine, haloperidol, paroxetine and metoclopramide use increased significantly during hospitalization.

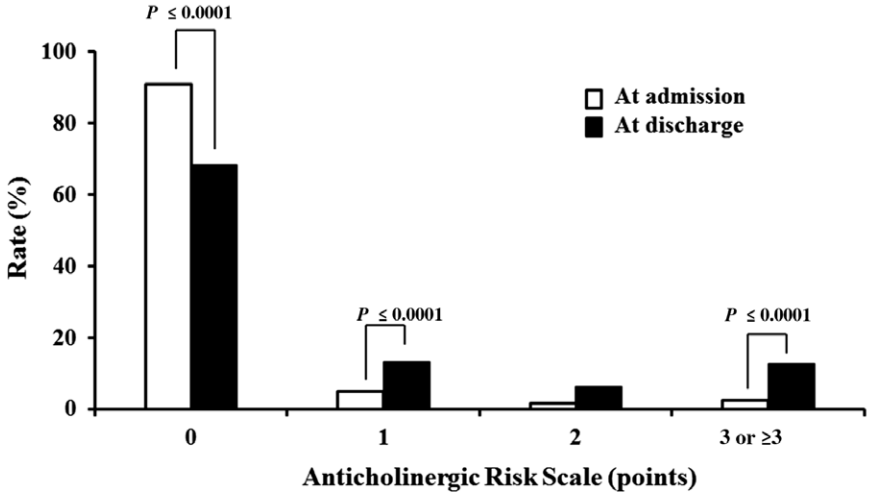

Figure 1 Comparison of the Anticholinergic Risk Scale at admission and discharge. The McNemar test was used to compare the Anticholinergic Risk Scale at admission and discharge, n = 601.

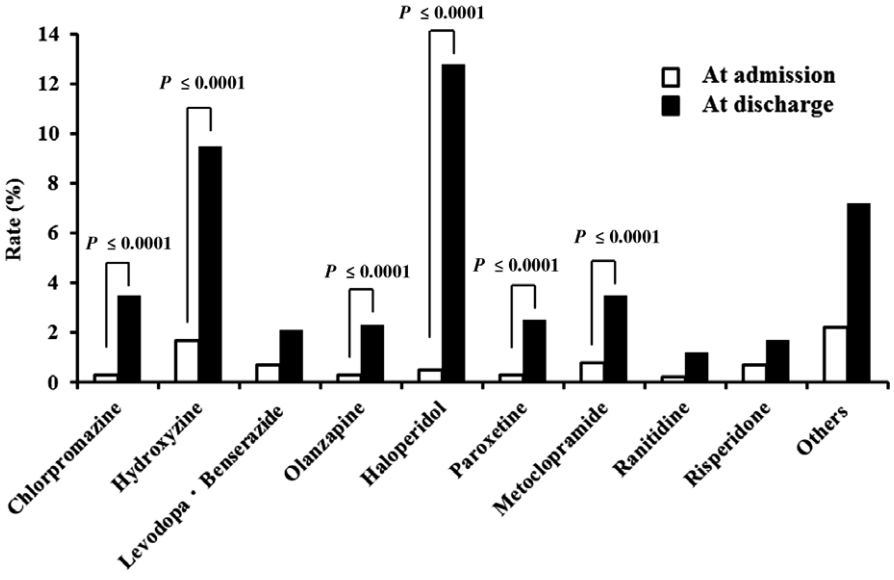

Figure 2 Comparison of anticholinergic drugs prescribed at admission and discharge. The McNemar test was used to compare anticholinergic drugs prescribed at admission and discharge.

Risk of hip fracture by the change in the ARS score

Table 3 shows the risk of hip fracture by each score of ARS change during hospitalization. The risk increased 1.57-fold for 1 point (95% CI 0.683–3.331, $P = 0.2706$), 2.86-fold for 2 points (95% CI 0.941–6.874, $P = 0.0409$) and 4.21-fold (95% CI 2.815–7.562, $P \leq 0.0001$) for ≥3 points, respectively, in ARS score change. The risk of hip fracture was significantly increased for 2 points and ≥3 points in ARS score change.

Discussion

The most important finding of the present study was that among older adults admitted to a convalescent rehabilitation ward, the incidence of hip fracture correlated with the change in the ARS score during hospitalization. In other words, during hospitalization, the risk of hip fracture might increase with an increase in the total anticholinergic load. Furthermore, a 2-point increase in the ARS score significantly increased the risk of hip fracture by 2.9-fold, whereas a ≥3-point increase in the ARS score increased the risk by 4.2-fold. Thus, we showed that the concurrent use of drugs with strong anticholinergic activity or even an addition of a drug with weak anticholinergic activity can increase the intensity of anticholinergic activity, influencing the incidences of hip fracture.

Only a few reports have examined the association between anticholinergic drugs and the risk of fracture; however, Chatterjee *et al.* found that high-level anticholinergic use was more associated with fracture risk than non-use.[7] Thus, the present results were in concordance with those previously reported. Additionally, Chatterjee *et al.*[7] reported that the risk of fractures remained consistent across levels of anticholinergic potency. The present study differs from the previous report in that we found the risk of fracture increases in accordance with the cumulative load of the anticholinergic drug. A previous report showed that in older individuals, the sensitivity to anticholinergic activity is increased[20] as a result, the cumulative administration of anticholinergic drugs increases the risk of onset of adverse drug events, as evidenced by the present results.[13,21] Therefore, in older individuals, caution should be exercised when administering drugs with potent anticholinergic activity or a combination of anticholinergic drugs.

In the present study, the ARS scores increased from admission through discharge; notably, the proportion of participants with ARS scores of ≥3 points increased by 12.5%. From admission to discharge, the proportion of participants using chlorpromazine and hydroxyzine, whose ARS scores were 3 points, increased by 3.2% and 7.8%, those of participants using olanzapine, whose ARS scores were 2 points, increased by 2%, and those of participants using haloperidol, paroxetine and metoclopramide, whose ARS scores were 1 point, increased by 12.3%, 2.2% and 2.7%, respectively. These drugs act on the central nervous system, and have been reported to directly inhibit the nervous system responsible for controlling drowsiness, sedation and swallowing, thereby causing motor dysfunction and sensory disturbance of the oral cavity and pharynx. Furthermore, anticholinergic drugs not only reduce the level of consciousness, such as by inducing sedation and drowsiness, similar to that of drugs acting on the central nervous system, but also reduce the amount of salivary secretion, causing mouth dryness. Furthermore, in our earlier study, we reported that in the convalescent rehabilitation ward, increased anticholinergic load during hospitalization restricted activities of daily living "eating" items.[22] In the present study, univariate analysis showed no significant difference in GNRI at admission between the fracture and non-fracture groups. However, at discharge, GNRI was significantly lower in the fracture group than in the non-fracture group. Furthermore, the proportion of individuals with GNRI <92 was significantly higher in the fracture group than in the non-fracture group. Also, it has been reported that malnutrition increases the risk of fracture.[23] As is evident from the above, increased anticholinergic load reduces the amount of salivary secretion, causing mouth dryness, and thereby resulting in reduced food intake and drug-induced malnutrition, which are believed to be associated with the onset of hip fracture. Therefore, in patients who are administered anticholinergic drugs, the options of dose reduction or termination should be examined. However, even if the drugs are suspected to be the underlying cause for the fracture, it is difficult to identify the drug that is associated with the increased risk of fracture when using combination therapy. In several instances, drugs are administered when required; therefore, their discontinuation should be considered with special attention to possible exacerbation of the underlying disease after termination. In particular, a previous report showed that the sudden discontinuation of antipsychotics exacerbates the preliminary symptoms, which emphasizes the need for due care

Table 3 Risk for hip fracture by increased Anticholinergic Risk Scale score

ARS (points)	OR	95% CI	*P*-value
0	1.00	Reference	NS
1	1.57	0.683–3.331	0.2706
2	2.86	0.941–6.874	0.0409
≥3	4.21	2.815–7.562	<0.0001

ARS, Anticholinergic Risk Scale; CI, confidence interval; NS, not significant; OR, odds ratio.

when reducing or discontinuing the dosage.[24] It is preferable that anticholinergic drugs should not be readily administered to older adults.

Several key strengths should be highlighted. First, Chatterjee *et al.* could not monitor the change in the ARS scores.[7] In the present study, we were able to track the changes in the ARS scores from admission to discharge, which forms the strength of the present study. Second, Chatterjee *et al.* targeted older individuals with depression, thereby limiting the study sample.[7] However, the present study targeted the older adult population and thus the results obtained can be generalized. Third, factors, such as use of steroids,[25] which are believed to increase the risk of fracture, and a history of osteoporosis, falls during hospitalization, nutritional status, BW and physical activity were not examined in the previous report.[7] In the present study, the results were adjusted for these confounding factors. Fourth, as shown in earlier reports, we showed that the cumulative administration of anticholinergic drugs increases the risk of adverse events.[13,21] Therefore, the present findings are of great clinical significance in terms of drug selection to prevent hip fractures in a convalescent rehabilitation ward, which hosts particularly elderly patients at a high risk of fracture from falling.

The present study had several limitations. First, this was a retrospective study design; therefore, the causal relationship could not be clarified in the results. Second, electronic medical charts-recorded information was used to capture data, and it could not be verified whether participants took the dispensed medicine. Third, the drug dosage was not considered. Fourth, as the present study was a retrospective observational study, the temporal relationship between increased ARS score and hip fracture is unknown; that is, whether or not the hip fracture occurred after the ARS score increase. Finally, the effects of anticholinergic drugs other than those examined by Rudolph *et al.* were not considered.[13]

In conclusion, the present study showed that a change in the ARS score is associated with the incidence of hip fracture, and that the risk of onset increases in conjunction with the level of increase in the ARS score. In the future, further examination is warranted to determine the extent to which dosage reduction or termination of anticholinergic drugs can reduce the incidence of hip fracture.

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Disclosure statement

The authors declare no conflict of interest.

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