Risk of Falls in Alzheimer’s Disease: A Prospective Study

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Abstract

Objective  Falls are common in patients with Alzheimer’s disease (AD). Identification of the potential risk factors and developing preventive strategies for falls will have a significant impact in maintaining the quality of life in AD.

Patients  Clinical follow-up of 124 (74.1±6.1 years, range 62–88) mild to moderate AD patients in an outpatient memory clinic.

Methods  Postural sway, cognitive function, use of neuroleptics, severity of periventricular and deep white matter lesions, and the presence or absence of silent brain infarctions on magnetic resonance imaging were assessed at baseline.

Results  A total of 104 patients (84%) completed the study. Fall events were confirmed in 42.3% (44/104). After adjustment for age, gender, and cognitive status, a high grade of periventricular white matter lesions (odds ratio 8.7 [95% CI 1.5 to 51.8], p=0.017) and neuroleptic drug use (odds ratio 3.5 [95% CI 1.2 to 10.5], p=0.027) were significantly associated with an increased risk of falls.

Conclusion  Our results suggest that periventricular white matter lesions and the use of neuroleptics may be related to falls in mild to moderate AD. A comprehensive risk management of brain ischemia as well as the use of the smallest efficacious dose of neuroleptics in the treatment of behavioral and psychiatric symptoms of AD should be recommended to help reduce the risk of unexpected falls.

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Key words:  Alzheimer’s disease, falls, white matter lesions, neuroleptics, silent brain infarctions

Introduction

Falls are common in elderly people and often lead to fracture, loss of mobility, and permanent bed-ridden state. It has been noted that older people with cognitive impairment are more likely to suffer falls (1, 2). In fact, the fall rate in patients with Alzheimer’s disease (AD) was reported to be approximately 2 times higher than age-matched control subjects (3). Sudden falls may lead to an early institutionalization and an increase in medical expenditure even in AD patients whose cognitive function can be fairly stabilized with the benefit of cholinesterase inhibitors. Although defects in attention and/or visuospatial abilities may explain why AD patients are less likely to avoid path obstacles and are more at risk of falling, the neurobiological basis for an increased risk of falling remains less understood. A series of studies have demonstrated that cerebral white matter lesions may relate to cognition and postural balance (4–6). Therefore, early detection of cerebral white matter lesions and development of preventive strategies for falls may have a significant impact in maintaining the quality of life in AD.

In the present study, we conducted a clinic-based, prospective study to relate postural balance and falls to the severity of periventricular and deep white matter lesions, the presence or absence of silent brain infarctions on magnetic resonance imaging, as well as cognitive function and neuroleptic drug use.

Methods

Study population  We examined 124 outpatients (74.1±6.1 years, range 62–88) who were diagnosed as having probable AD according to the NINCDS-ADRDA criteria (7). These patients were enrolled through both the Tohoku University Hospital Outpatients Clinic for dementia at the Department of Geriatric Medicine and the Kodama Hospital between April
1998 and March 2000. All patients were living at home and could walk without support. They underwent standardized medical and neuropsychological examinations as well as a baseline evaluation of demographic data including age, gender, use of neuroleptic drugs and concurrent illnesses. History on the use of neuroleptic drugs including haloperidol, risperidone, chlorpromazine hydrochloride, thioridazine hydrochloride, thiapride hydrochloride and sulpiride was collected at 1-month intervals upon entry into the study. To assess and estimate cognitive function, Mini-Mental State Examination (MMSE) was administered at baseline. The baseline MMSE scores were 16.2±5.9 points (range 8–25).

Primary caregivers were asked by E.H. if falls occurred upon every visit to our outpatient clinic during the year following enrollment into the study. Visits were scheduled every 14 days. Confirmed fall events were defined as “falling all the way down to the floor or ground” given by the patient’s family members and/or other reliable collateral sources. Written informed consent to participate in the study was provided by a responsible caregiver. Our study protocol was approved by the ethical review committee at the Tohoku University School of Medicine.

MRI scanning

MRI scanning was performed on a 1.5 Tesla superconducting magnet. Transverse T1-weighted, T2-weighted and FLAIR images were obtained with a slice thickness of 5 mm. Silent brain infarctions were defined as 1) spotty areas and FLAIR images were obtained with a slice thickness of 5 mm. Silent brain infarctions were defined as 1) spotty areas 3 mm in diameter showing high intensity in the T2-weighted and low intensity in the T1 weighted images; 2) lack of neurological signs and/or symptoms that could be explained by the MRI lesions; 3) no medical history of clinical stroke confirmed by a family member or other reliable collateral source as shown in our previous studies (6, 8). Small punctate hyperintensity lesions with a diameter of 1–2 mm were more likely to represent dilated perivascular spaces and were not considered here. Most silent brain infarctions were few in number with a diameter less than 10 mm and usually located in the basal ganglia or adjacent deep white matter. Deep white matter lesions (DWMLs) were specified as a high intensity area in the FLAIR and T2-weighted images but nearly isointense with normal brain parenchyma in the T1-weighted image as described previously (9). The DWMLs were located subcortically but not adjacent to lateral ventricle. The other type of white matter lesions that were adjacent to the lateral ventricle were defined as periventricular white matter lesions (PWMLs). The severity of DWMLs was graded as 0 (absent), 1 (punctate), 2 (beginning confluent) and 3 (large confluent), and that of PWMLs as 0 (absent), 1 (thin lining or small foci) and 2 (smooth halo or thick lining) by visual rating scale according to the method described by Fazekas et al (10). No fresh cerebrovascular lesions were confirmed in any patients during follow-up.

Posturography measurements

Measurements of sway by posturography were assessed with a stationary stable level biomechanics force plate (model GS-2000 Gravicorder, Anima Corporation, Tokyo). The force plate consists of a flat surface beneath which are three vertical force transducers proportional to the applied force. Patients stood on the force plate bare footed and in Romberg’s foot position. Before the measurements of sway, patients were asked to keep standing on the platform comfortably, looking at a fixation point straight ahead with their head erect and, arms hanging at their side. The fixation point was placed at subjects’ eye level and the distance was approximately 1.5 m in front of the subject. The standard test protocol included the measurements of sway for 60 seconds with eyes open, and then another 60 seconds with eyes closed. Data were excluded when patients were not able to obey instructions, taking a step ahead or backward, or moving vigorously. The force plate measures the relative vertical loading of weight to calculate the center of pressure (COP). The standard deviation for the lateral and forward-backward directions of postural sway was calculated, and the root mean square (RMS) for the deviations from the mean position served as the extent of postural sway (COP-RMS).

Statistical analysis

Statistical analyses were carried out with the statistical software package SPSS version 10.0. Continuous variables were compared by ANOVA with Dunnett’s posthoc analysis. Categorical variables were compared by $\chi^2$ testing. Multiple logistic regression models were used to estimate adjusted odds ratio (95% CI) of falls. Statistical significance was set at $p<0.05$.

Results

Of the 124 patients, 84% (104/124) completed the one-year follow-up; 42.3% (44/104) reported falls during that year, and 6.8% (3/44) of the fallers experienced fractures in the hip joint (n=3) and in the lower leg (n=1). Two patients died during the follow-up period. Of the 44 fallers, 75% (33/44) reported a single fall, whereas other patients reported two or more falls. The clinical and neuroimaging profiles in fallers and non-fallers are given in Table 1. In the univariate analysis, the fallers were significantly older ($p=0.047$), had a significantly higher frequency of neuroleptic drug use ($p=0.012$) and a higher grade of PWMLs ($p=0.015$). However, gender distribution ($p=0.574$), body mass index ($p=0.590$) or severity of dementia ($p=0.359$) as expressed by MMSE scores were not significantly different between fallers and non-fallers. There was a tendency toward more frequent falls in patients with silent brain infarction ($p=0.096$) as well as in patients with a higher grade of DWMLs ($p=0.128$), but it did not reach statistical significance. The COP-RMS values were significantly larger ($p=0.001$) in the fallers (0.94±0.26 cm) compared to the non-fallers (0.77±0.22 cm).

As shown in Fig.1, the COP-RMS values were significantly larger in groups with grade 1 (0.934±0.276) and grade...
2 (0.899±0.257) PWMLs compared to grade 0 PWMLs (0.745±0.194). The COP-RMS values also were significantly different (p=0.01) between groups with (0.913±0.250) or without (0.800±0.245) silent brain infarction. However, the COP-RMS values did not differ significantly according to the use (0.872±0.206) or non-use (0.835±0.265) of neuroleptics (p=0.56). Finally, there was no significant correlation between the MMSE scores and the COP-RMS values (r=–0.044, p=0.64).

As mentioned in Table 2, after adjustment for age, gender and cognitive status, logistic regression model showed that grade 2 PWMLs (odds ratio 8.7 [95%CI 1.5 to 51.8], p=0.017) and neuroleptic drug use (odds ratio 3.5 [95%CI 1.2 to 10.5], p=0.027) were significantly associated with an increased risk of falls.

Of the neuroleptic drug users (n=25), tiapride hydrochloride was used most commonly (n=15) and 11 of the 15 tiapride users experienced falls. Treatment period did not differ significantly between tiapride users and non-users (292±178 day vs. 220±145 days, p=0.48). When tiapride users were divided into two groups according to the dosage, the fall rates were 77.8% (7/9) in the higher dosage group (between 75 mg and 150 mg a day) and 66.7% (4/6) in the lower dosage group (between 25 mg and 50 mg a day), respectively (p=0.538 by Fisher’s exact test). In 19 neuroleptic drug users in which neurological examination was completed, 47.4% (9/19) users developed parkinsonian motor features. However, there was no significant association (p=0.30 by Fisher’s exact test) between falls and Parkinsonism.

**Discussion**

In the present study, the risk of fall in AD patients was examined by two different methods, i.e. posturography and MRI imaging of ischemic brain lesions. Here, we provide two major findings. First, periventricular white matter lesions may disturb postural balance and lead to an increased risk of falls in AD. FLAIR and T2-weighted images of MRI enabled us to define the presence and the severity of distinct ischemic brain lesions. Second, neuroleptic drugs most commonly used in the treatment of behavioral and psychiatric symptoms of dementia were also associated with an increased risk of falls, but did not appear to affect postural balance. Therefore, it is likely that ischemia-related falls may be caused by a different mechanism than neuroleptics-based falls. Since a variety of vascular risk factors such as hypertension (9, 11) and high plasma homocysteine levels (8, 11) are associated with an increased risk of developing white matter lesions and silent brain infarctions, the incidence of falls may be reduced by managing potential vascular risk factors. Furthermore, as soon as the behavioral and psychiatric problems are resolved, tapering or discontinuation of neuroleptics should be considered in order to reduce the risk of falls. This is an additional reason for recommending the use of the smallest efficacious dosage of neuroleptics in the treatment of behavioral and psychiatric symptoms of dementia.

The etiology of white matter lesions remains largely unknown. The periventricular region contains numerous long projecting fibers that connect the cortex with subcortical nuclei and more distant cortical areas, whereas the subcortical region has abundant short looped U-fibers that connect...
adjacent cortical areas. Therefore, it is likely that peri-
ventricular white matter lesions may disrupt long associating
fibers that connect distant cortical areas. Fazekas et al (12)
related histopathological changes associated with incidental
white matter signal abnormality on MRI and found that caps
or a smooth halo of periventricular white matter lesions are
linked to disruption of the ependymal lining, subependymal
gliosis and concomitant loss of myelin due to altered
periventricular fluid dynamics. Importantly, they noted that
irregular periventricular white matter lesions extending into
deep white matter also indicate atherosclerotic change of a
similar degree as present with confluent deep white matter
lesions (12). Therefore, grade 2 periventricular white matter
lesions should be regarded as ischemic, and these lesions
may disturb multiple neural networks that are essential to
maintain postural balance.

It is unclear why neuroleptic drug users fall approximately
3 times more frequently than non-users despite the fact that
the users apparently maintain postural balance. Stolze et al
(13) reported that Parkinson’s disease patients most fre-
cently fall within a variety of neurological disorders. In this
report, Parkinson’s disease patients having akinetic and
freezing episodes were most likely to fall. Therefore, we
speculate that current posturography measures (which rely
on an increase in COP-RMS values to indicate an increased
risk of falls) may not adequately reflect akinetic and freezing
postures which are often induced by typical neuroleptics
with a dopamine D2 receptor antagonist.

There are limitations in our study. First, although we
showed that both fall events and COP-RMS measures did not
relate to the severity of dementia, severely demented AD pa-
tients with MMSE scores below 8 points were not included

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**Figure 1.** Center of pressure (COP)-Root mean square (RMS) (COP-RMS) values were plotted accord-
ing to the grade of periventricular white matter lesions (A), the presence or absence of silent brain in-
farction (B), use or non-use of neuroleptics (C), and dementia severity measured by mini-mental state
examination (MMSE) (D). Bars represent mean values.
here because of incomplete and less reliable posturography measures due to multiple cognitive impairments. Therefore, it is possible that falls in severely demented patients can be explained alternatively. In our previous study, postural and gait disturbances in severe stages of dementia were associated with a reduced cerebral blood flow in the frontal lobe (14). A second limitation of the present study is the difficulty in verifying the fall history because AD patients may not adequately remember each fall or caregivers may not be aware of every fall event. However, the fall rate in the present study (42.3%), while likely an underestimate, is comparable to previous estimates in a different population of AD patients (3). Therefore, potential underreporting is not likely to be a major limitation. A third limitation was that data were lacking on other classes of psychoactive drugs including anti-depressants and benzodiazepines. Although anti-depressants and benzodiazepines are reported to be associated with an increased risk of falls (13, 15, 16), the small sample size of patients regularly taking drugs other than neuroleptics prohibited such analysis.

In conclusion, our results suggest that ischemic periventricular lesions and use of neuroleptics, but not disease progression, may be related to falls in mild to moderate AD. A comprehensive risk management of brain ischemia as well as use of the smallest efficacious dosage of neuroleptics in the treatment of behavioral and psychiatric symptoms of AD should be recommended to reduce the risk of falls and to maintain a good quality of life.

References


