表4　急性期病棟における月平均の行動制限患者数（人）

	2008年度	2009年度	2010年度	2011年度	2012年度
隔離	0.3	0.3	1.2	0.4	0.8
身体拘束	0.1	0.3	0.3	0.0	0.3

表5　1日当たりの身体抑制の件数（急性期病棟，2013年）

	1月	2月	3月	4月	5月	6月
ベッド柵	1.4	0.9	1.2	0.4	1.1	1.4
板テーブル	2.0	3.0	2.8	2.3	1.3	1.7
安全ベルト	7.3	7.7	4.9	4.5	4.7	4.8
ミトン	0.6	0.2	0.0	0.5	1.7	1.8
つなぎ服	1.0	1.0	1.0	0.7	0.0	0.0
月末入院患者数	44	48	47	44	46	42

表6　1ヵ月間に身体抑制が行われた実人数（認知症病棟，2013年）

	1月	2月	3月	4月	5月	6月
ベッド柵	10	9	8	8	7	8
板テーブル	2	1	1	1	1	1
安全ベルト	2	2	2	2	2	3
ミトン	0	0	1	0	0	0
つなぎ服	0	3	0	3	2	1
月末入院患者数	48	47	46	47	46	48

表7　転倒・転落に関するインシデント・アクシデント件数（件）

	2010年度		2011年度		2012年度	
	インシデント	アクシデント（うち転院）	インシデント	アクシデント（うち転院）	インシデント	アクシデント（うち転院）
急性期病棟	41	6 (3)	26	6 (1)	39	11 (4)
認知症病棟	27	1 (0)	30	4 (2)	28	2 (0)

（ ）内は骨折による転院

8件は大腿骨骨折で手術後再入院となった。2件は急性硬膜下血種を伴う頭蓋骨骨折で，他者とは関係なく後方に転倒したケースであり，予後不良であった。

Ⅳ．考　察

BPSDは主に環境への不適応で生じるといわれている。したがって，隔離や身体拘束，身体抑制などの通常ありえない状況下に認知症の人を置けばBPSDが悪化するのは自明であり，したがって認知症の人に対する行動制限はほとんど治療的な意味はないと考える。先に示した通り，当院でも認知症の人に対してはほとんど隔離や身体拘束は行っておらず，むしろ作業療法やレクリエーション活動などに積極的に参加してもらい，集団行動を望まない人にはトラブルがない限り終日病棟内を歩き回ってもらうなどして，できるだけ自然な

状況での療養を心掛けている。我々は，入院治療の目的を短期集中的なBPSDの治療と考えており，BPSDが軽減すれば，できるだけ速やかに元の居所へ退院するのが当然と考えている。そのような立場では，退院の妨げとなるのはBPSDに対する治療効果よりもむしろ心身両面の廃用症候群の悪化である。特に自宅への退院を目指す場合には，歩行機能が低下したらチャンスは少なくなる。

しかしながら，BPSDの顕著な認知症の人を治療する場合，特に抗精神病薬などを用いた際は，転倒，転落に対する防止策が重要なのはいうまでもない。我々は長年にわたる認知症の治療を通じ，転倒，転落防止の方法を講じてきた。そして何が法の身体拘束に当たり，何が当たらないかもスタッフ間で協議してきた。安全ベルトや板テーブルの使用をすべて身体拘束にすべきであるという意見もあったが，指定医の業務が著しく増大する上，診療録への記載が煩雑になるため，むしろそれらを身体拘束とした場合に解除への取り組みが少なくなる懸念があった。最終的には法の身体拘束とは別に，5つの手技を身体抑制と定義し，看護手順を定めるに至った。また時間帯ごとの病棟の見回り方法なども何度も協議し，工夫している。それでも先に挙げたような重大な転倒事故を完全に防ぐことはできておらず，さらなる手技の向上が必要である。

重要なことは，認知症の人に対してなされる行動制限が，安全面や治療面で本人のためになっているかということである。主語は常に「認知症の人」であるべきで，「業務が忙しく看ていられない」といったことは行動制限の理由にならない。そしてもう一点重要なことは，全職員が行動制限の最小化を常に意識しているかということである。そのためには多職種が情報を共有し，ミーティングでの合議を通じ対応を一定にしなければならない。何よりも家族へ繰り返し説明することにより行動制限の意識化が図られると思う。

ところで，身体拘束や身体抑制を行っている限り，介護施設へは入所できない。当院では，認知症病棟でベッド4点柵を使用していたため，介護保険施設の入所を断られることが何度かあり，介護保険施設の入所を目指す人には一切身体抑制を行わずに経過をみる必要があることを思い知った。つまり精神科病院が認知症の人にとっての終の棲家ではなくBPSD治療のための一時的な入院であることに徹すれば，自ずから行動制限は減ると愚考する。

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White-Matter Hyperintensities Predict Delirium After Cardiac Surgery

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Objectives: *Postoperative delirium is a common psychiatric disorder among patients who undergo cardiac surgery. Although several studies have investigated risk factors for delirium after cardiac surgery, the association between delirium and cerebral white-matter hyperintensities (WMH) on magnetic resonance (MR) imaging has not been previously studied. The aim of this study was to identify general risk factors for delirium, as well as to examine the specific relationship between WMH and delirium.* **Design:** *Retrospective chart review.* **Setting:** *University hospital.* **Participants:** *A total of 130 patients who underwent cardiac surgery.* **Measurements:** *Variables recorded included patient demographics, comorbidities, mental health, laboratory data, surgical information, and cerebrovascular disease. The presence of WMH was assessed using MR images. Two groups of patients were compared (patients with and without delirium) using both univariate and multiple logistic analyses.* **Results:** *Delirium occurred in 18 patients (13.8%) and patients with delirium were significantly older than patients who did not develop delirium. The prevalence of severe WMH (Fazekas score = 3) was significantly higher in patients with delirium. Three independent predictors of delirium were identified: abnormal creatinine (odds ratio [OR]: 4.5; 95% confidence interval [CI]: 1.4–13.9), severe WMH (OR: 3.9; 95% CI: 1.2–12.5), and duration of surgery (OR: 1.4; 95% CI: 1.0–1.8).* **Conclusions:** *The results of this study suggest that white-matter abnormality is one of the most important risk factors for development of delirium after cardiac surgery. These factors can be used for prediction and prevention of delirium following cardiac surgery.* (Am J Geriatr Psychiatry 2013; 21:938–945)

Key Words: Cardiac surgery, delirium, magnetic resonance imaging, white matter

Delirium is an acute state of confusion characterized by disturbed consciousness and cognitive dysfunction. Delirium is a complication of many physical disorders and is a common postoperative state, particularly among hospitalized patients.[1] The development of delirium after surgery has been associated with prolonged hospital stays, increased costs, and increased mortality.[2–4]

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As medical techniques continue to evolve, the patient population eligible for cardiac surgery will continue to expand to include even *older adults* and patients with other risk factors including hypertension, diabetes, heart failure, hyperlipidemia, severe angina, and emergent surgery.[5–7] These populations are particularly susceptible to the development of delirium in the postoperative period. Some studies have demonstrated beneficial effects of early pharmacologic intervention and intensive nursing care on the severity and duration of postoperative delirium.[8,9] Moreover, one study indicated that early pharmacological intervention reduced the number of days in the hospital.[8] Therefore, prevention or early recognition of delirium is an important goal.

Previous studies have demonstrated high rates of ischemic change in the brains of patients with cardiac disease.[10,11] Several studies have shown that white matter hyperintensities (WMH), identified on brain magnetic resonance (MR) imaging, represent cerebral ischemic change and neural degeneration.[12,13] In recent years, several researchers have suggested that WMH are related to mental disorders, such as cognitive dysfunction in older patients, and late-life depression.[14–19] Some of these studies suggest a relationship between WMH and specific cognitive deficits such as attention deficits, processing speed decrease, and executive function deficits.[15,16,18] Some other studies also suggest that WMH predict worse outcomes in patients with depression.[17,19] Although several studies have identified risk factors for delirium after cardiac surgery,[20–29] the association between delirium and cerebral WMH has not been thoroughly examined. Therefore, the hypothesis of this study is that WMH are associated with the development of delirium, with symptoms including both cognitive and emotional disturbance. The objectives of this study were to identify risk factors for postoperative delirium in patients who have undergone cardiac surgery and to examine the relationship between WMH and delirium.

METHODS

Participants

A total of 164 patients underwent cardiac surgery between April 2009 and March 2010 at Kyoto Prefectural University of Medicine (KPUM). To evaluate for the presence of cerebrovascular disease and to rule out organic brain diseases, cardiovascular department guidelines call for preoperative brain and carotid artery MR scans in all patients scheduled to undergo cardiac surgery. All MR scans were performed prior to surgery at KPUM. Among the 164 eligible patients, 29 were excluded because brain MR images were not obtained (19 patients did not undergo MR imaging due to acute admission and 10 patients had a previous brain MR from another institution). An additional five patients were excluded, namely, two patients with delirium before surgery, two patients who had undergone reoperation for graft repair, and one patient who died soon after surgery. The single patient who had a stroke after surgery was included in this study. Three patients with mental disorders such as mental retardation, epilepsy, and mild depression were also included in the analysis. In total, 130 participants who underwent cardiac surgery were analyzed using retrospective chart review. Patient characteristics (age, sex ratio, and type of surgery ratio) were not significantly different between patients who were included and excluded from this study (Appendix 1). The study was approved by the institutional review board at KPUM.

Clinical Variables

Clinical and laboratory data were obtained from medical charts and, with the exception of MR image assessment, all variables were reviewed by HY (lead author). Potential risk factors for postoperative delirium were selected on the basis of previously published literature.[20–29] Risk factors assessed included patient demographics, comorbidities, mental health, laboratory profile both prior to and after surgery, type and duration of surgery, and cerebrovascular disease. In all patients, the presence of hypertension, hyperlipidemia, diabetes, atrial fibrillation, and arteriosclerosis obliterans was recorded. Mental health information included the presence of mental disease, a history of use of psychotropic medications, and/or use of anxiolytics, including benzodiazepines, zolpidem, and zopiclone. Other medications such as steroids, H_2 receptor antagonists, and hydroxyzine were also included. Body mass index was collected from the preoperative anesthesia record. The last preoperative and first postoperative

laboratory values were used; these included the albumin level, hematocrit, blood urea nitrogen, and creatinine. Types of surgery were categorized as coronary artery bypass graft surgery (CABG), off-pump coronary artery bypass graft surgery (OPCAB, bypass surgery without the use of cardiopulmonary bypass), valve replacement/repair with/without CABG, and other. The "other" category included maze procedures with CABG, maze procedures with valve replacement/repair, ventricular septal defect closures, and Bentall procedures. Cerebrovascular disease was recorded using the presence of carotid artery stenosis, a prior stroke or transient ischemic attack, and degree of WMH. Carotid artery stenosis was defined as either moderate or severe stenosis and the degree of stenosis was diagnosed under blinded conditions by a trained radiologist (YK) using MR angiography.

Delirium Assessment

The diagnosis of delirium was made from medical charts reviewed under blinded conditions by trained psychiatrists (Y. Hatano and Y. Hata). Mental status descriptions in the medical record were most often entered by the treating physician and/or primary nurse. However, mental status descriptions made by consulting psychiatrists were also reviewed. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* diagnostic criteria were used to define delirium.[30] Interrater reliability was calculated using intraclass correlation coefficients (ICCs). There was good reliability between raters for the assessment of delirium (ICC: 0.883; 95% CI: 0.835–0.917).

Magnetic resonance. All patients in this study were scanned using a 1.5 T whole-body scanner (Gyroscan Intera; Philips Healthcare, Best, the Netherlands). The routine brain imaging protocol at our institute requires 14 minutes and consists of T1-weighted images (repetition time: 611 ms; echo time: 13 ms), T2-weighted images (repetition time: 4754 ms; echo time: 100 ms), and fluid level-attenuated inversion recovery images (delay time: 2200 ms; repetition time: 8000 ms; echo time: 100 ms). Time-of-flight MR angiography (repetition time: 30 ms; echo time: 2.3 ms) is also routinely included in the protocol.

MR Scan Analysis

MR images were randomized and assessed under blinded conditions by two authors (MT and TS) using T2-weighted images and fluid attenuated inversion recovery. WMH were assessed using the modified Fazekas criteria.[31] The Fazekas criteria describe WMH on MR imaging in three regions and follow an ascending degree of severity and frequency for hyperintensities. Deep white-matter hyperintensities (DWMH; 0: absent; 1: punctate foci; 2: initial confluence of foci; 3: large confluent area) and periventricular hyperintensities (PVH; 0: absent; 1: caps; 2: smooth halo; 3: irregular with extension into deep white matter) were assessed. Interrater reliability was calculated separately using ICCs. Interrater reliability calculations showed good agreement (DWMH ICC: 0.884; 95% CI: 0.836–0.918; PVH ICC: 0.882; 95% CI: 0.832–0.916).

Table 1 presents grades of baseline WMH in all 130 patients analyzed in this study. The results of this study demonstrated a 96.2% prevalence of DWMH and a 100% prevalence of PVH among participants. Indeed, 21.5% of patients had severe DWMH (n = 28) and severe PVH was found in 39.2% of patients (n = 51).

Statistical Analysis

All variables were compared between two groups (patients with delirium and patients without delirium). Student's *t*-test was used for continuous variables, and the χ^2 test was used for dichotomous variables. If an expected frequency was less than 5, Fisher's exact test was used for analysis. Variables that demonstrated a different prevalence between the two groups ($p < 0.1$) were entered into a logistic regression analysis. Continuous variables that demonstrated a nonlinear correlation with the presence or absence of delirium were converted into dichotomous variables. For example, creatinine was categorized as either normal ($\leq$1.1 mg/dL) or abnormal (>1.1 mg/dL), and albumin was categorized as either normal ($\geq$3.9 g/dL) or abnormal (<3.9 g/dL), based on local clinical guidelines from KPUM. Patient age was also dichotomized into two groups (age: <70 or $\geq$70 years) based on criteria suggested in previous studies.[20,26] Using the Fazekas score, DWMH and PVH were divided into two groups (severe: Fazekas score = 3; moderate or less: Fazekas score = 0–2). For a logistic regression analysis, a forward selection method (likelihood ratio) was used to determine the predictors of delirium. A p value of <0.05 was used to enter and eliminate variables. Goodness of fit was determined using the

TABLE 1. Baseline Grades of White-Matter Hyperintensities

Fazekas Score	Delirium (n = 18)	Percent	No Delirium (n = 112)	Percent
Deep white-matter hyperintensities				
0	0	0.0	5	4.4
1	5	27.8	44	39.3
2	5	27.8	43	38.4
3	8	44.4	20	17.9
Periventricular hyperintensities				
0	0	0.0	0	0.0
1	1	5.6	31	27.7
2	6	33.3	41	36.6
3	11	61.1	40	35.7

Hosmer–Lemeshow test. The capacity to distinguish between patients with and without delirium was estimated using the area under the receiver operating characteristic (ROC) curve. Statistical data were analyzed with SPSS version 19.0 (IBM, Armonk, NY). Fisher's exact test was performed in tables larger than 2 × 2 using R version 2.1 (http://www.r-project.org/).

RESULTS

Demographic and medical characteristics of patients are shown in Table 2. The mean age of the patient population was 66.6 ± 10.9 years, with 41.5% of the population older than 70 years (n = 54). Eighty-nine (68.5%) patients were men. Fifty-seven patients (43.8%) underwent valve replacement or repair with or without CABG and 43 patients (33.1%) underwent OPCAB. Delirium occurred in 18 patients (13.8%).

The prevalence of delirium did not vary significantly among the four types of surgeries. Although there was no significant difference between patient groups, the average length of postoperative hospital stay in patients with delirium (35.4 ± 37.0 days) was longer than in patients without delirium (18.5 ± 7.5 days; p = 0.071). There were no patients with head injuries during the study period.

Results of univariate analysis comparing candidate predictor variables of delirium between patients with and without delirium are shown in Table 2. Patients with delirium were significantly older and patients with arteriosclerosis obliterans were significantly more likely to develop delirium. The prevalence of severe WMH was significantly higher in patients with delirium. Patients with delirium had a significantly higher prevalence of pre- and postoperative lower albumin and higher creatinine values. Patients whose surgical procedures were of a longer duration tended to develop delirium. To avoid confounding by multicollinearity, postoperative creatinine values that demonstrated a strong correlation with preoperative creatinine values (Spearman's $r = 0.83$; $p < 0.01$) were excluded. There was also a high correlation between the DWMH Fazekas scores and the PVH Fazekas scores (Spearman's $r = 0.77$; $p < 0.01$). Therefore, the DWMH Fazekas score was chosen for further analysis as the DWMH Fazekas score ($p = 0.041$) demonstrated better differentiation between groups (DWMH: $p = 0.041$; PVH: $p = 0.026$).

A multiple logistic analysis identified three independent predictors of postoperative delirium: abnormal creatinine (OR: 4.5; 95% CI: 1.4–13.9), severe DWMH (OR: 3.9; 95% CI: 1.2–12.5), and duration of surgery (OR: 1.4; 95% CI: 1.0–1.8) (Table 3). The Hosmer–Lemeshow test showed that the goodness of fit for the final prediction model containing these three factors was strong ($p = 0.37$; a high p value indicates better fit). The area under the ROC curve was also calculated using the model. The area under the curve was 0.82 (95% CI: 0.73–0.91; $p < 0.001$).

DISCUSSION

This study identified that severe DWMH predicts delirium after cardiac surgery. Other independent predictors of delirium were identified, including abnormal creatinine and duration of surgery. A final predictive model including these three predictors showed a high degree of reliability and the capacity to correctly classify patients into two groups: those with delirium and those without delirium.

WMH represent diffuse areas of brain white-matter loss associated with local increases in brain water

TABLE 2. Univariate Analysis of All Candidate Predictor Variables

Characteristics	Delirium (n = 18)		No Delirium (n = 112)		p
Age, mean (SD), years	**71.3**	**(8.5)**	**65.9**	**(11.1)**	**0.05**[a]
≥ 65 years	**12**	**(67)**	**42**	**(38)**	**0.02**[b]
Sex, women, n (%)	4	(22)	37	(33)	0.43[c]
Types of surgery, n (%)					0.66[c]
CABG	1	(6)	6	(5)	
OPCAB	4	(22)	39	(35)	
Valve with or without CABG	10	(56)	47	(42)	
Other	3	(17)	20	(18)	
Psychotropic drug use, n (%)	4	(22)	23	(21)	1.00[c]
Anxiolytic use, n (%)	4	(22)	20	(18)	0.74[c]
Steroid (predonizolone), n (%)	0	(0)	3	(3)	1.00[c]
Hydroxyzine, n (%)	1	(6)	0	(0)	0.14[c]
H_2 receptor antagonist, n (%)	2	(17)	20	(83)	0.74[c]
Hypertension, n (%)	14	(78)	81	(72)	0.78[b]
Hyperlipidemia, n (%)	9	(50)	54	(48)	0.89[b]
Diabetes mellitus, n (%)	9	(50)	39	(35)	0.22[b]
Prior stroke/TIA, n (%)	4	(22)	18	(16)	0.51[c]
Carotid artery stenosis, n (%)	4	(22)	23	(21)	1.00[c]
Arteriosclerosis obliterans, n (%)	**3**	**(17)**	**4**	**(4)**	**0.06**[c]
Atrial fibrillation, n (%)	6	(33)	19	(17)	0.11[b]
Preoperative infection, n (%)	0	(0)	2	(2)	1.0[c]
Postoperative infection, n (%)	2	(11)	3	(3)	0.14[c]
Severe DWMH (Fazekas score 3), n (%)	**8**	**(44)**	**20**	**(18)**	**0.03**[b]
Severe PVH (Fazekas score 3), n (%)	**11**	**(61)**	**40**	**(36)**	**0.04**[b]
Body mass index, mean (SD)	22.6	(3.9)	22.4	(3.3)	0.82[a]
LVEF (%), mean (SD)	58.8	(14.9)	61.8	(11.1)	0.31[a]
Albumin <3.9 g/dL, n (%)	**7**	**(39)**	**19**	**(17)**	**0.05**[b]
Creatinine >1.1 mg/dL, n (%)	**10**	**(56)**	**23**	**(21)**	**0.03**[b]
Hematocrit <36%, n (%)	9	(50)	37	(33)	0.16[b]
Blood urea nitrogen (mg/dL), mean (SD)	19.6	(9.1)	18.8	(8.0)	0.71[a]
Albumin <3.9 g/dL (postoperative), n (%)	**18**	**(100)**	**94**	**(84)**	**0.08**[b]
Creatinine >1.1 mg/dL (postoperative), n (%)	7	**(39)**	**16**	**(14)**	**0.02**[b]
Hematocrit <36% (postoperative), n (%)	17	(94)	97	(87)	0.35[b]
Blood urea nitrogen (mg/dL) (postoperative)	16.0	(9.1)	15.7	(6.5)	0.86[b]
Duration of surgery, mean (SD), hour	**8.3**	**(2.2)**	**6.7**	**(1.9)**	**0.001**[a]

Notes: Boldface text/values indicate the variables that demonstrated a different prevalence between the two groups and p value was less than 0.1 (p <0.1). CABG: coronary artery bypass graft surgery; DWMH: deep white-matter hyperintensities; LVEF: left ventricular ejection fraction; OPCAB: off-pump coronary artery bypass graft surgery; PVH: periventricular hyperintensities; TIA: transient ischemic attack.

[a]Student's *t*-test.

[b]Chi-square test.

[c]Fisher's exact test.

content.[12] WMH are commonly observed on brain MR images of elderly patients.[32,33] Several studies have demonstrated the association between WMH and vascular risk factors.[12,34,35] Recent studies have shown that the major factor in the pathogenesis of WMH is cerebral arteriosclerosis of the small vessels.[12] Several studies have suggested that patients with higher grades of WMH are more likely to develop psychiatric disorders such as depression or cognitive dysfunction.[14–19] However, little literature exists on the association between white-matter abnormalities and delirium. Recently, Shioiri et al.,[24] using a diffusion tensor imaging method, showed that abnormalities in several white-matter regions predisposed patients to delirium after cardiac surgery. However, the association between WMH and delirium was not mentioned. This study suggests the possibility that higher grades of WMH predispose patients to developing delirium through white-matter deterioration. The pathogenesis

TABLE 3. Multiple Logistic Regression Analysis for Predictors of Postoperative Delirium

Variable	Odds Ratio	95% CI	p
Creatinine >1.1 mg/dL	4.5	1.4–13.9	0.01
Severe DWMH (Fazekas score 3)	3.9	1.2–12.5	0.02
Duration of surgery, hour	1.4	1.0–1.8	0.02

of postoperative delirium is associated with several etiologies.[1] Inflammatory response syndrome and hypermetabolism are induced by surgery under general anesthesia. The inflammatory response syndrome is known to stimulate macrophage enzymes and excess enzyme activity leads to oxidative stress, which can cause dysregulation of central neuronal function. Central nervous system resident cells react to the presence of peripheral immune signals, leading to the production of cytokines and other mediators in the brain. Neuroinflammation promotes a cholinergic deficit with associated imbalances in other neurotransmitters, including dopamine, serotonin, and norepinephrine.[36] Delirium develops via neurotransmitter dysfunction in several subcortical structures such as the amygdala and hippocampus, which are connected through basal ganglia-thalamo-cortical loops.[1]

A postmortem study showed that WMH correspond to heterogeneous pathologies with varying degrees of myelin attenuation, arteriolosclerosis, and gliosis.[13] These pathologic changes in white-matter pathways may be factors that induce delirium by promoting the vulnerability of the central nervous system.

Abnormal creatinine values and prolonged duration of surgery were also identified as predictive factors for the development of delirium, in agreement with previous studies.[22,27,29] Renal dysfunction frequently reflects the presence of several secondary diseases, including poorly controlled hypertension, hypoalbuminemia, and cerebrovascular disease.[29] These factors may contribute to developing delirium by impairing metabolism and promoting neuronal dysfunction. A prolonged duration of surgery has also been implicated as a risk factor for delirium.[22] During the intraoperative period, there are several potential factors (e.g., fluid balance, urine output, body temperature, anesthetic time, and time on cardiopulmonary bypass [CPB]) that may play a role in the development of delirium.[21] In particular, an association between prolonged duration of CPB and delirium has been shown.[22,29] However, in this study, the prevalence of delirium was not significantly different when the OPCAB group was compared with other surgical groups that required CPB (OPCAB: 9.3%; CPB: 16.1%; $p = 0.42$). The effects of prolonged anesthetic time on the potential for developing delirium are also controversial.[22] Further investigation is needed to identify specific intraoperative factors that predispose a patient to developing delirium.

There was a high prevalence of baseline WMH in patients in this study (Table 1). Greater than half of the included patients had white-matter lesions of moderate or severe hyperintensity (Fazekas score = 2 or 3). These results support other previous studies, which have indicated higher rates of ischemic changes in the brain of patients with cardiac disease than in people without cardiac disease.[10,11,32,33] In addition, recent studies have shown that patients with cardiac disease are more likely to have baseline cognitive impairment and the association between cerebral ischemic change and cognitive impairment has also been shown.[10,37] These results indicate that patients with cardiac disease have a tendency toward increased cerebral vulnerability, which leads to the development of neuropsychiatric complications, including cognitive dysfunction and delirium.

The results of this study must be viewed in light of its limitations. This study employed a retrospective analysis in which the quality of medical information depends on descriptions provided by treating physicians or nurses. Therefore, it is possible that the prevalence of delirium is underestimated in this study. No rating scales were used to assess delirium. However, the diagnosis of delirium and WMH assessments were conducted carefully by two blinded psychiatrists and the strength of the results are supported by the interrater reliability values, demonstrating a high degree of agreement. In terms of cognitive function, because of the retrospective design, we did not assess any rating of cognitive function and diagnosis of dementia. Several studies have suggested that cognitive impairment was one of the major risk factors for the development of delirium in older adults.[21,24] Therefore, a prospective study might be needed to examine the degree of effect of cognitive impairment on the development of delirium compared with other factors, including WMH.

In conclusion, severe DWMH was identified as a predictor for the development of delirium following cardiac surgery. Other predictors of delirium were abnormal creatinine values and duration of surgery. These factors can be used for prediction and prevention of delirium. In addition, this study identified a high baseline prevalence of WMH in patients

with cardiac disease. Further prospective studies are needed to validate a clinical prediction rule based on the risk factors identified in this study. Future studies are also needed to investigate the pathogenesis of delirium using volumetric analysis of specific regions of WMH.

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APPENDIX 1. Demographics of patients included and excluded

Characteristics	Included (n = 130)		Excluded (n = 30)		p
Age, (mean (SD), years	66.6	10.9	64.3	14.3	0.32
Sex, women, n (%)	41	(32)	12	(40)	0.40
Types of surgery, n (%)					0.43
CABG	7	(5)	4	(13)	
OPCAB	43	(33)	8	(27)	
Valve with or without CABG	57	(44)	14	(47)	
Other	23	(18)	4	(13)	

Notes: CABG: coronary artery bypass graft surgery; OPCAB: off-pump coronary artery bypass graft surgery.

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ORIGINAL RESEARCH

Treatment in a ward for elderly patients with dementia in Japan

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Background: Japan has become the world's most aged country. The percentage of elderly people in Japan is estimated to reach 25.2% in 2013, and the number of patients with dementia is estimated to reach 2.5 million in 2015. In addition to its deterioration of physical function and activities of daily living (ADL), behavioral and psychological symptoms of dementia (BPSD) often become major clinical problems, greatly annoying patients and their caregivers. In Japan, we utilize wards for elderly patients with dementia (WEDs) for BPSD treatment. However, there are few studies investigating the effectiveness of treatment in a WED. In such treatment, physical complications are a challenge physicians must overcome while treating BPSD and safely returning patients home or to the institutions in which they live. Therefore, we investigated the effectiveness of treatment in a WED, focusing on physical complications.

Methods: The subjects were 88 patients who were admitted to and discharged from a WED. Severity of dementia, basic ADL, and BPSD were investigated using the Clinical Dementia Rating, Physical Self-Maintenance Scale (PSMS), and Neuropsychiatric Inventory. Differences in characteristics between patients discharged from the WED because of physical complications and all other patients were also examined.

Results: We found significant improvements in the PSMS score and decreases in delusions and sleep disturbances in all patients. Patients discharged from the WED because of physical complications had significantly greater severity of dementia at discharge compared to all other patients.

Conclusion: Treatment in a WED seems to be effective for BPSD and ADL, but care should be taken regarding physical complications, especially in patients with advanced dementia.

Keywords: aged country, behavioral and psychological symptoms of dementia, physical complications, activities of daily living

Introduction

According to the *White Paper on the Aging Society*, Japan became the world's most aged country in 2005, overtaking Italy in terms of the rate of elderly people, and is expected to enter an era of an "unprecedented" aging society in the future.[1] The estimated rates of elderly people are 31.6% for 2030 and 39.9% for 2060.[2] The prevalence of dementia has increased as people are aging,[3,4] and patients with dementia are projected to number 2.5 million in 2015 and 3.2 million in 2025.[5] During the course of illness, behavioral and psychological symptoms of dementia (BPSD) often become major clinical problems for patients and their caregivers, and sometimes lead to hospitalization. To treat BPSD, special wards for elderly patients with dementia (WEDs) were introduced in Japan in 1988. The staff in these wards constitute a multidisciplinary team comprising

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a psychiatrist, experienced nurses, an occupational therapist (OT), and a psychiatric social worker (PSW) or psychologist. Each professional evaluates the patients and provides treatment based on their specialty, such as medication, care and nursing, coordination of social circumstances, recreation, and group psychotherapy.

Several studies have shown the effectiveness of BPSD treatment at special acute units for people with dementia in Western countries.[6,7] In contrast, few studies have examined the course of BPSD during a stay in a WED in Japan. Therefore, we conducted a retrospective analysis of patients who were admitted to a WED, with a focus on physical complications, because these often interrupt treatment and lead to transfer to another hospital.[8] Ukai et al[9] and Ukai and Mizuno[10] found a high frequency of physical complications in a WED that required treatment by specialists of other medical departments, and Ono et al[11] reported that physical complication was a predictor of a longer stay in a WED. Therefore, to identify risk factors related to physical complications, we compared the characteristics of patients transferred to another hospital or ward because of physical complications with those of all other patients. In addition, we investigated the effect of the use of antipsychotics on dementia severity, basic activities of daily living, and BPSD.

Methods

Subjects and procedure

We performed a retrospective chart review of 88 patients with dementia who were admitted to the WED at Umibeno-mori Hospital, Kochi, Japan between June 1, 2008 and May 31, 2009 and were discharged by January 1, 2010. The WED staff consists of a full-time psychiatrist, experienced nurses, a full-time OT, and a full-time PSW. In the WED, treatment includes medication and education about dementia and BPSD provided by the psychiatrist, care and nursing by the experienced nurses, preparation of social support by the PSW, and rehabilitation by the OT. The Umibeno-mori Hospital WED provides patients a familiar environment in addition to medication. For example, there are kitchens and a living room with televisions and sofas. Tansu (Japanese traditional cabinets) and tatami (Japanese traditional mats) are in patients' private rooms, and staff members put on casual clothing so as to provide patients a homelike atmosphere in an attempt to moderate their anxiety, strain, and wariness. Moreover, patients are provided with recreational activities such as hiking and tea groups so that they can have an enjoyable time and keep a regular daily rhythm, to prevent disuse syndrome, and to moderate BPSD. We provide group psychotherapy such as life reviews to stimulate their cognitive functions. Above all, since there are only elderly patients in the WED, conversation and communication happen naturally between them. All patients were admitted from home, an institution, or other wards at Umibeno-mori Hospital or other hospitals and were discharged to home, an institution, or other wards or hospitals.

We made the final diagnosis of dementia at discharge based on the text version of the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*).[12] Standardized clinical diagnostic criteria were used to characterize the type of dementia. Diagnoses of Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) were made in accordance with NINCDS-ADRDA,[13] NINDS-AIREN,[14] and DLB consensus criteria described by McKeith et al,[15] and FTD consensus criteria described by Neary et al,[16] respectively.

Demographic and clinical data were collected from charts. The severity of dementia was evaluated using the Clinical Dementia Rating (CDR),[17] basic ADL was determined using the Physical Self-Maintenance Scale (PSMS),[18] and the presence of BPSD was established using the Neuropsychiatric Inventory (NPI)[19] at admission and discharge. The CDR is an observation scale for the assessment of six domains – memory, orientation, judgment, community affairs, home and hobbies, and personal care – with scoring as follows: CDR 0, healthy; CDR 0.5, questionable dementia; CDR 1, mild dementia; CDR 2, moderate dementia; and CDR 3, severe dementia. The PSMS consists of six items on the performance of the physical activities of using the toilet, self-feeding, self-dressing, self-grooming, self-ambulating, and self-bathing, with a lower total score indicating more ADL impairment. The NPI is a clinical instrument with which the caregiver evaluates the patient's 12 domains of neuropsychiatric symptoms in dementia: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, and eating problems.

All chart reviews were performed by one rater (ST). The interrater reliability was established through independent rating by a skilled rater (NA) of 10 randomly sampled subjects. The interrater intraclass correlation coefficients were 0.96 and 0.96 for the CDR and 0.80 and 0.76 for the PSMS at admission and discharge, respectively, and the kappa statistics for each NPI subscale were 0.8–1.0. This study was approved by the Umibeno-mori Hospital ethical committee and was performed in compliance with the principles of the Declaration of Helsinki. Patient records were used carefully and anonymously.

Statistical analysis

To investigate the effectiveness of treatment in the WED, we compared the scores for the CDR and PSMS and the presence of each NPI subscale at admission with those at discharge via a Wilcoxon signed rank test and a χ^2 test. We also compared the characteristics of patients transferred to other wards or other hospitals because of physical complications with those of all other patients by using a Mann–Whitney *U*-test for continuous variables and a χ^2 test for categorical data. In addition, we compared the CDR and PSMS scores and the number of patients with BPSD both at admission and discharge between patients who were prescribed antipsychotics and those who were not prescribed antipsychotics by using a Mann–Whitney *U*-test for continuous variables and a χ^2 test for categorical data. Data were analyzed using SPSS (v12.0 J) for Windows (IBM Corporation, Armonk, NY, USA). A P-value < 0.05 was considered significant. A Bonferroni correction was used to correct for multiple comparisons.

Results

The characteristics of the 88 patients (44 males, 44 females) are shown in Table 1. AD was the most common diagnosis (AD, 61%; vascular dementia, 18%; DLB, 5%; FTD, 1%; others, 17%). Psychotropic prescriptions did not differ significantly at admission and discharge. About half of the patients were prescribed antipsychotics at admission. The number of patients with some physical complications increased slightly at discharge. At admission, there were no patients with severe physical complications requiring treatment at other wards or hospitals, but about one-third of patients had severe physical complications at discharge.

The PSMS score at discharge was significantly higher than that at admission, whereas the CDR score did not change significantly (Table 2). Regarding the presence of each NPI item (Figure 1), about 33% of patients had agitation, aberrant motor behavior, and sleep disturbances at admission. At discharge, there were large decreases in the percentages of patients with delusions and sleep disturbances and decreases in other NPI items, except for depression, euphoria, and irritability.

Table 3 shows a comparison of the characteristics of 29 patients transferred to other wards or hospitals because of physical complications and 59 patients discharged without severe physical complications from the WED to home, an institution, or another ward or hospital. There was a significant difference in the CDR score at discharge between these groups, but not for other characteristics, including the use of antipsychotics.

Table 1 Clinical characteristics of all patients at admission and at discharge from the WED

Characteristics (n = 88)	At admission	At discharge
Mean age (SD)	81.3 (7.08)	
Gender (male/female)	44/44	
Diagnosis		
AD		54
VD		16
DLB		4
FTD		1
Others		13
Residence		
Home	33	18
Institution	17	26
Other hospital	18	22
Other ward	20	22
Mean length of stay, days (SD)		70.9 (70.7)
Median length of stay, days		49
Psychotropic prescriptions		
Antipsychotics	47	48
Risperidone	11	12
Olanzapine	3	3
Quetiapine	16	16
Perospirone	10	10
Aripiprazole	1	1
Typical antipsychotics	11	11
Benzodiazepine	12	11
Antidepressants	18	15
Mood stabilizers	20	23
Acetylcholinesterase inhibitors	27	22
Physical complications	69	75
Severe physical complications	0	29
Pneumonia	0	8
Fracture	0	3
Urinary infection	0	3
Chronic subdural hematoma	0	2
Others	0	13

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; SD, standard deviation; VD, vascular dementia; WED, ward for elderly patients with dementia.

Table 4 shows the comparison of the CDR, PSMS scores, and the number of patients with BPSD between patients who were prescribed antipsychotics and those who were not prescribed antipsychotics at admission and at discharge. There were no significant differences; however, the CDR scores of patients who were prescribed antipsychotics tended

Table 2 CDR and PSMS scores (mean ± SD) at admission to and at discharge from the WED

	At admission	At discharge	*P*-value
CDR score	2.34 ± 0.78	2.27 ± 0.82	NS
PSMS score	1.07 ± 1.10	1.33 ± 1.22	0.002*

Notes: Wilcoxon signed rank test; *Bonferroni-corrected $P < 0.01$.
Abbreviations: CDR, clinical dementia rating; NS, not significant; PSMS, physical self-maintenance scale; WED, ward for elderly patients with dementia.

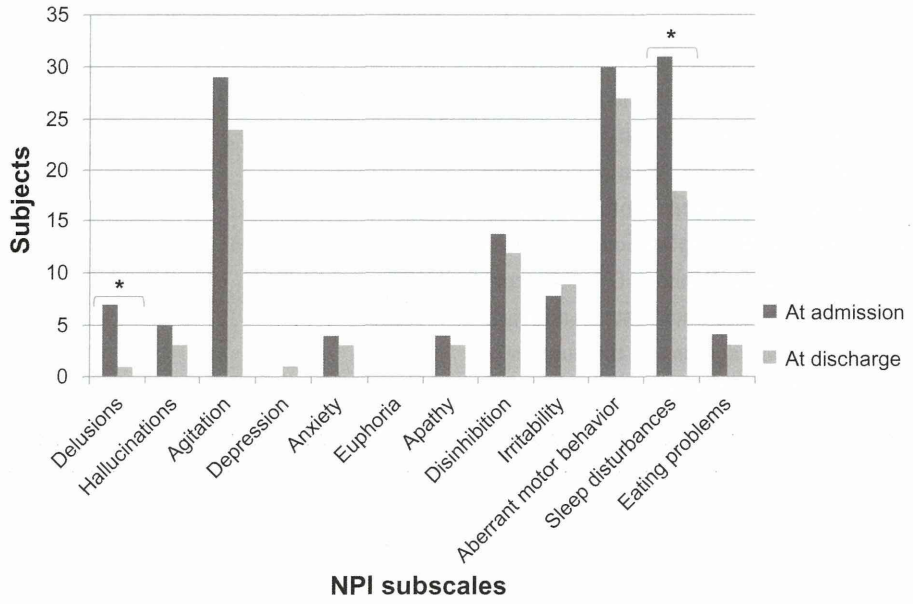

Figure 1 NPI subscale rates in 88 patients with dementia at admission to the ward for elderly patients with dementia and at discharge from same.
Notes: Almost all NPI subscale rates had decreased at discharge, especially for delusions and sleep disturbances. *Uncorrected $P < 0.05$, Bonferroni-corrected $P > 0.05$.
Abbreviation: NPI, Neuropsychiatric Inventory.

to be worse than those of patients who were not prescribed antipsychotics at discharge.

Discussion

In this study, we used a retrospective chart review to investigate the utility of treatment in a WED and the characteristics of patients related to physical complications. The WED treatment significantly improved basic ADL and tended to decrease most BPSD, especially delusions and sleep disturbances. Patients transferred to other wards or hospitals because of physical complications had higher CDR scores at discharge. These results show the value of treatment in a WED and also indicate a relationship between the severity of dementia and the occurrence of physical complications.

The improvement of BPSD through treatment of elderly people with dementia in special care units has been shown in previous studies, in which Bellelli et al[6] found an overall reduction in behavioral disturbances and Colombo et al[7] showed significant improvement of each element of BPSD. Our results are consistent with these studies and suggest that the treatment provided in a WED in Japan is effective in ameliorating BPSD. In regard to the reduction effect for delusions and sleep disturbances, we first considered the direct effects of medications. Second, as we explained in the

Table 3 Comparison of characteristics between patients discharged from the WED because of severe physical complications and those discharged without severe physical complications

	Discharge without severe physical complications	Discharge with severe physical complications	*P*-value
Number	59	29	
Mean age at admission (years)	81.6 ± 6.0	81.2 ± 8.2	NS
CDR at admission	2.41 ± 0.79	2.62 ± 0.56	NS
CDR at discharge	2.03 ± 2.03	2.66 ± 0.61	0.002*
PSMS at admission	1.07 ± 1.08	0.76 ± 0.58	NS
PSMS at discharge	1.62 ± 1.35	0.83 ± 0.83	0.009**
Physical complications at admission (yes/no)	46/13	23/6	NS
Prescription of antipsychotics at discharge (yes/no)	34/25	14/15	NS

Notes: Mann–Whitney *U*-test; Chi-square distribution; *Bonferroni-corrected $P < 0.05$; **uncorrected $P < 0.05$, Bonferroni-corrected $P > 0.05$.
Abbreviations: CDR, clinical dementia rating; NS, not significant; PSMS, physical self-maintenance scale; WED, ward for elderly patients with dementia.

Table 4 Comparison of the CDR and PSMS scores (mean ± SD) and number of patients with BPSD between patients who were prescribed antipsychotics and those who were not prescribed antipsychotics at admission and at discharge

	Patients who were prescribed antipsychotics	Patients who were not prescribed antipsychotics	*P*-value
Number at admission	47	41	
CDR score at admission	2.4 ± 0.74	2.1 ± 0.86	NS
PSMS score at admission	0.95 ± 0.97	1.1 ± 1.2	NS
Number of patients with BPSD at admission	44	39	NS
Number at discharge	48	40	
CDR score at discharge	2.4 ± 0.86	2.0 ± 0.73	0.04*
PSMS score at discharge	1.1 ± 1.2	1.6 ± 1.2	NS
Number of patients with BPSD at discharge	36	27	NS

Notes: Mann–Whitney *U*-test; Chi-square distribution; *uncorrected $P < 0.05$, Bonferroni-corrected $P > 0.05$.
Abbreviations: BPSD, behavioral and psychological symptoms of dementia; CDR, clinical dementia rating; NS, not significant; PSMS, physical self-maintenance scale.

Methods section, supportive behavior by experienced staff members in the WED and familiar environments moderated their anxiety, strain, and wariness. Moreover, recreation, conversation, and communication between elderly patients contributed to stabilizing their mental states and regular daily rhythms. Hence, medications and the treatment environment in the WED might be effective for BPSD, especially relative to delusions and sleep disturbances. Regarding admission, Soto et al[20] reported that the main cause of admission to a special acute care unit for elderly people with dementia was aggressiveness and that the frequencies of wandering and sleep disorders were high. Ono et al[21] found that the major causes of admission to the WED were violence and wandering in men and wandering and care distress in women. In this study, the rates of agitation, aberrant motor behavior, and sleep disturbances were higher than those for other NPI items at admission, and these symptoms had decreased at discharge. This finding suggests that treatment in a WED addresses the symptoms that are mainly responsible for admission to the WED. However, many symptoms were still present at discharge, which indicates the importance of reducing BPSD further and supporting caregivers for coping with patients with dementia and BPSD.

Regarding the treatment itself, about half of the patients were prescribed antipsychotics both at admission and discharge. This suggests the persistent use of antipsychotics for BPSD in Japan, even after reports of an increased risk of mortality with the use of antipsychotics in people with dementia.[22,23] The rate of use of antipsychotics did not differ significantly between patients transferred to other wards or hospitals because of physical complications and other patients; however, the CDR scores of patients who were prescribed antipsychotics tended to be worse than those of patients who were not prescribed antipsychotics at discharge. We consider it is possible that side effects of antipsychotics, such as anticholinergic and sedative effects, cause cognitive impairment in patients with dementia; we should thus prescribe antipsychotics carefully and make an effort to reduce the number of antipsychotic prescriptions we write. In contrast, we found a significant improvement in ADL. Thus, the multidisciplinary approach to the maintenance of ADL during the WED stay, including rehabilitation conducted by an OT, appears to be effective and may even improve ADL. Relatively shorter lengths of hospitalization may also have contributed to this result, since Yoshie et al found improved ADL levels for patients hospitalized for less than 1 year.[24] Collectively, our results indicate that treatment in a WED is effective for ameliorating BPSD without worsening ADL.

About one-third of the patients had severe physical complications that led to referral to other wards or hospitals. The prevalence of severe physical complications is comparable to that in a previous report.[25] Patients discharged because of physical complications had more impaired cognitive disorders than other patients. Physical complications have often been shown to be a common and serious problem in elderly patients with dementia. For example, Mitchell et al reported that pneumonia, febrile episodes, and eating problems were frequent complications in patients with advanced dementia and were associated with high 6-month mortality rates.[26] We should interpret the results in this study carefully, because it is possible that physical complications themselves cause cognitive impairment to patients with dementia. However, we believe that this study adds some knowledge about the relationship between physical complications and dementia severity, and we suggest that care should be taken regarding

physical complications, especially in patients with advanced dementia.

The mean and median lengths of hospitalization in this study were 71 and 49 days, respectively, which are shorter than those in other WED studies. Kitamura et al[27] reported median stays of 87 days for men and 74 days for women; Mizuno[28] found a rate of discharge within 3 months of 30%–40%; Yoshie and Shiraishi[23] reported mean and median stays of 353.4 days and 129.6 days, respectively; Ono et al[11] reported a median stay of 103 days; and Matsubara[29] found that almost 85% of patients in wards specifically used for dementia treatment stayed for more than 91 days. The short length of hospitalization in this study might be due to the close relationships between the hospital and nearby institutions, which allow the relocation of patients to these institutions after BPSD improvement. Thus, social work is important to maintaining the function of a WED as an acute treatment unit for BPSD.

The results of this study must be interpreted with caution according to several limitations. First, it might be difficult to generalize the results of this study because there might be a slight difference between treatment in our hospital and in other hospitals. However, the aim and standard treatment in the WED is basically common in Japan based on regulation of WEDs, and we provided general treatment in the WED at Umibeno-mori Hospital. Second, the study was conducted retrospectively, and data obtained from chart reviews, physicians' estimations, and nurses' reports might be inaccurate. Third, the sample size was small. Fourth, the relationship between the severity of dementia and the occurrence of physical complications is controversial in this study, as described above. Fifth, different characteristics of patients with dementia (eg, ADL and BPSD) and their diagnosis might confound the treatment's effectiveness. Furthermore, we evaluated only the presence of BPSD and did not consider BPSD severity.

Conclusion

The present results suggest that treatment in a WED improved the ADL of patients with dementia and BPSD, particularly in terms of delusions and sleep disturbances. Patients who were discharged from the WED for treatment of severe physical complications had more impaired cognitive disorders compared to those who were discharged without severe physical complications. Since there have been few studies investigating the state and effectiveness of WEDs in Japan, we believe that this study adds some knowledge about the treatment provided by WEDs. Multicenter prospective studies are necessary to examine the effectiveness of treatment in a WED in a large number of patients with dementia whose characteristics are matched at baseline.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL RESEARCH

Diagnostic performance of a combination of Mini-Mental State Examination and Clock Drawing Test in detecting Alzheimer's disease

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Objective: Because of the growing need for quick cognitive screening tests to distinguish Alzheimer's disease (AD) from mild cognitive impairment (MCI), we compare the diagnostic performance of a combination of the Mini-Mental State Examination (MMSE) and a Clock Drawing Test (CDT) to the Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-J cog) in differentiating between patients with AD, patients with MCI, and healthy controls (HC).

Methods: Data from 146 subjects with AD and 60 subjects with MCI, as well as 49 HC, was retrospectively analyzed. We used logistic regression analysis with diagnosis as dependent variables and scores of the MMSE, the CDT-command, and the CDT-copy as independent variables, and receiver operating characteristic analysis to distinguish patients with AD from patients with MCI or HC.

Results: When patients with AD were compared to HC, the independent predictors of AD were scores on the MMSE and the CDT-command. This combination was more sensitive than the MMSE alone and has nearly the same sensitivity and specificity as the ADAS-J cog. When patients with AD were compared to patients with MCI, the independent predictors were the MMSE and the CDT-copy. This combination was more sensitive and specific than the MMSE alone and was almost as sensitive and specific as the ADAS-J cog.

Conclusion: The combination of the MMSE and the CDT could be a powerful screening tool for differentiating between patients with AD, patients with MCI, and HC. Its sensitivity and specificity are comparable to ADAS-J cog, which takes more time.

Keywords: diagnostic techniques, Alzheimer's disease, mild cognitive impairment, Clock Drawing Test, Mini-Mental State Examination

Introduction

Following the introduction of the concept of mild cognitive impairment (MCI),[1] general practitioners are frequently required to follow patients diagnosed with MCI and decide whether patients convert from MCI to Alzheimer's disease (AD). This distinction is essential to starting treatment, including the prescription of cholinesterase inhibitors, in a timely fashion. Considering that MCI has been defined as presence of cognitive impairment among intact daily functions, accurate assessment of functional status is important to detect the conversion from MCI to AD. Although performance-based assessments are ideal measures for functional status, they are difficult to administer in busy primary care settings. Instead, cognitive tests that are quick and easy to administer are feasible for general practitioners.

Although several screening instruments are available for detecting dementia, the Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT) have

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been widely used, particularly as quick cognitive screens for dementia in the primary care setting.[2] Both the MMSE and the CDT are reported to be sensitive in identifying cognitive impairments. A recent meta-analysis of 34 dementia studies and five MCI studies suggested MMSE had a modest sensitivity of 77% and a specificity of 90% for application in high-prevalence specialist settings and a sensitivity of 81% and a specificity of 87%.[2] Although CDT varies in scoring, a comprehensive literature review suggested that all CDT scorings are remarkably consistent, and both sensitivity and specificity levels have a mean of 85%.[3] However, the MMSE, in combination with the CDT, has an improved diagnostic performance (sensitivity, 82%–100%; specificity, 83.9%–95.4%), and it is recommended as an easily administered and accurate instrument.[4–7] Together, these two assessments take about 10 minutes to perform.

In contrast, the Japanese version of the AD Assessment Scale cognitive subscale (ADAS-J cog) is predominantly used in randomized controlled trials that examine the symptomatic benefits of therapy for AD.[8,9] The ADAS-J cog consists of eleven tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities, which are often referred to as the core symptoms of AD. It is useful as an instrument for evaluating dementia in a specialized psychogeriatric outpatient setting. However, it takes more than 30 minutes to perform and is thus difficult to use when time is limited.

In this study, we sought to compare diagnostic performance of a combination of the MMSE and the CDT with the ADAS-J cog differentiating between patients with AD, patients with MCI, and healthy controls (HC). The goal was to clarify whether this combination would lead to higher or comparable accuracy than the ADAS-J cog.

Methods

Subjects

Subjects with MCI (n = 60) and AD (n = 146) were recruited from patients in the Aino Hospital. The diagnosis of MCI was made according to Petersen et al's criteria,[1] which corresponds to amnestic MCI by reported memory concerns, memory impairment on standard tests, absence of significant impairment in activities of daily living, and the absence of dementia. The diagnosis of AD was made according to the National Institute of Neurological and Communicative Disease and Stroke-Alzheimer's Disease and Related Disorders Association's (NINCDS-ADRDA) criteria for probable AD,[10] respectively. All subjects had been assessed comprehensively by a geriatric psychiatrist, received physical and neurological examinations, and reported their medical histories. Clinical data including functional status was confirmed by family members or other available caregivers. All pertinent laboratory tests and magnetic resonance imagings (MRIs) were reviewed.

HC (n = 49) were individuals living in the community who participated in the dementia prevention program provided by Aino Hospital. Exclusion criteria were a score of less than 25 on the MMSE,[11] and a score of less than 6 on the ADAS-J cog.[9] An interviewer had available access to the social workers in charge of each community before starting the dementia prevention program provided by Aino Hospital to confirm that HC led an independent life, with both basic and instrumental intact daily living activities.

This study was conducted at Aino Hospital and approved by the hospital's institutional review board. Informed consent was obtained from all subjects or from their substitute decision makers after receiving a complete description of the study.

Instruments

Subjects were interviewed by trained clinical psychologists with the CDT, the MMSE, and the ADAS-J cog.

CDT

For the CDT, subjects were presented with a blank sheet of paper and given the following instructions: "I would like you to draw a clock, put in all numbers, and set the hands for 10 past 11" (CDT-command). Next, they were presented with a drawing of a clock and asked to copy it (CDT-copy). The creators of the instrument, Rouleau et al,[12] scored subjects on a 10-point scale that is designed to assess the accuracy of the clock face representation (maximum 2 points), the layout of the numbers (maximum 4 points), and the position of the hands (maximum 4 points) independently.

MMSE

The MMSE[11] is a frequently used screening instrument in the evaluation of cognitive impairment. It consists of 30 points grouped into seven categories: orientation, registration, attention, calculation, recall, language, and visual construction.

ADAS-J cog

The ADAS-J cog[9] is generally considered the gold standard by regulatory authorities for assessing cognitive function in AD drug trials. It consists of 70 points, with higher scores indicating greater cognitive impairment, which are grouped into eleven categories: word recall, naming, commands, constructional praxis, ideational praxis, orientation, word

recognition, spoken language, comprehension, word finding, and remembering instructions.

Statistical analysis

Gender was compared using the Chi-square test. Age and scores of the MMSE, the CDT-command, the CDT-copy, and ADAS-J cog between patients with AD, patients with MCI, and HC were compared using one-way analysis of variance.

An analysis of covariance was used to compare scores from the MMSE, the CDT-command, the CDT-copy, and ADAS-J cog between patients with AD, patients with MCI, and HC, with age and gender as the covariates. Post hoc testing was performed using Tukey's honestly significant difference tests. Logistic regression analysis was used to optimize the classification performance of MMSE, CDT-command, and CDT-copy scores, namely, with diagnosis as the dependent variable and scores of the MMSE, the CDT-command, and the CDT-copy as the independent variables. Receiver operating characteristic analysis was used to compare diagnostic performance of the optimized combination with ADAS-J cog scores. Data was analyzed using the Statistical Package for the Social Sciences 17.0 (SPSS; IBM Corporation, Armonk, NY, USA), and resultant statistics where $P < 0.05$ were considered significant.

Results

Subjects' characteristics

The demographic characteristics with respect to age and gender for each group, along with MMSE, CDT-command, CDT-copy, and ADAS-J cog mean scores, are shown in Table 1. Mean age was significantly lower in HC as compared to patients with MCI and AD.

Diagnostic performance

The mean scores in all four neuropsychological tests (MMSE, CDT-command, CDT-copy, and ADAS-J cog) were significantly worse in the AD group as compared to the MCI group and HC (Table 1). After adjusting for the confounding variables of age and gender, AD patients had significantly worse performance in all neuropsychological tests (Table 2).

When the AD group was compared to the HC group, the areas under the curve (AUC) were 0.988 (confidence interval [CI] = 0.976–0.999) for MMSE ($P < 0.001$), 0.912 (CI = 0.871–0.952) for CDT-command ($P < 0.001$), 0.764 (CI = 0.700–0.829) for CDT-copy ($P < 0.001$), and 0.989 (CI = 0.979–1.000) for ADAS-J cog ($P < 0.001$). MMSE and CDT-command as identified by logistic regression analysis led to slightly higher values than MMSE alone, and values were nearly the same as those obtained with ADAS-J cog alone (0.997 [CI] = 0.987–1.000, $P < 0.001$), yielding a sensitivity of 91.1% and a specificity of 100.0%. The positive predictive value was 100.0% with the prevalence of AD at 74.9% in the sample (Table 3 and Figure 1). The equation used in logistic regression for differentiating between patients with AD and HC was:

$$52.67 - 1.49 \times \text{MMSE} - 1.39 \times \text{CDT-command}. \quad (1)$$

The AUC against the AD group and the MCI group were 0.795 (CI = 0.730–0.860) for MMSE ($P < 0.001$), 0.711 (CI = 0.630–0.792) for CDT-command ($P < 0.001$), 0.686 (CI = 0.614–0.759) for CDT-copy ($P < 0.001$), and 0.806 (CI = 0.741–0.871) for ADAS-J cog ($P < 0.001$). The best predictors of AD identified by logistic regression analysis were MMSE and CDT-copy. This combination led to slightly higher AUC than MMSE and was nearly the same as that obtained with ADAS-J cog (0.811 [CI] = 0.747–0.875, $P < 0.001$), yielding a sensitivity of 75.3% and a specificity

Table 1 Mean (SD) values for selected clinical variables by group

	HC (n = 49)	MCI (n = 60)	AD (n = 146)
Gender (male/female)	17/32	16/44	39/107
Age (years)	66.1 (8.0)	76.1 (9.2)[a]	79.1 (8.0)[a,d]
MMSE (score out of 30)	29.1 (1.2)	24.6 (4.1)[a]	19.1 (5.1)[a,b]
ADAS-J cog (score out of 70)	3.5 (1.6)	10.7 (6.1)[a]	19.2 (8.1)[a,b]
CDT-command (score out of 10)	9.5 (0.9)	7.6 (2.7)[a]	5.6 (2.7)[a,b]
CDT-copy (score out of 10)	10.0 (0.2)	9.7 (0.7)	8.2 (2.3)[a,b]

Notes: [a]$P < 0.001$ versus HC; [b]$P < 0.001$ versus MCI; [c]$P < 0.05$ versus HC; [d]$P < 0.05$ versus MCI.
Abbreviations: SD, standard deviation; HC, healthy controls; n, number; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; ADAS-J cog, Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale; CDT, clock drawing test.

Table 2 Mean (SD) ANCOVA values

	HC (n = 49)	MCI (n = 60)	AD (n = 146)
Adjusted for age and gender			
MMSE	28.1 (0.7)	24.6 (0.5)	19.4 (0.4)[a,b]
ADAS-J cog	4.8 (1.0)	10.7 (0.9)[a]	18.7 (0.6)[a,b]
CDT-command	9.0 (0.4)	7.6 (0.3)[c]	5.8 (0.2)[a,b]
CDT-copy	10.0 (0.3)	9.7 (0.2)	8.2 (0.2)[a,b]

Notes: [a]$P < 0.001$ versus HC; [b]$P < 0.001$ versus MCI; [c]$P < 0.05$ versus HC.
Abbreviations: SD, standard deviation; ANCOVA, analysis of covariance; HC, healthy controls; n, number; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; ADAS-J cog, Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale; CDT, clock drawing test.