quality clinical observation by psychiatrists in the general hospital setting, including fine dosage adjustment in individual patients and early detection of side effects, may have contributed in avoiding bad clinical course. So far, to our knowledge, there has no prospective observational study on the incidence of serious adverse events during antipsychotic treatment for delirium enrolling such a large number of patients in the general hospital setting under management by psychiatrists.

Although there is a retrospective cohort study utilizing insurance data sources (Wang *et al.*, 2005), causal relation between serious adverse events and antipsychotic treatment could not be specified from such data without close observation. In a meta-analysis of 15 randomized placebo-controlled clinical trials of atypical antipsychotic drugs to treat patients with Alzheimer disease or dementia, 118 deaths in the atypical antipsychotic drug groups and 40 in the placebo groups were summed up, which was a simple pooled incidence of 3.5% and 2.3% per trial, respectively (Schneider *et al.*, 2005). The locations in which the trials were performed were nursing homes (11 trials) or outpatient settings (4 trials), where high quality close observation by specialists could not have been expected. In such settings, relatively high incidence of death during antipsychotic treatment for older patients may have happened. Another explanation for the difference in outcome between the retrospective cohort study and the present study may be the length of antipsychotic treatment. In the former study, the administration of antipsychotics may have lasted for a long period because the target was behavioral symptoms with dementia. In contrast, the length of antipsychotic treatment in the present study was short, as delirium was resolved within 1 week in more than half of the patients. In a recent cohort study providing evidence of the risk of using antipsychotics in older residents in nursing homes, the rates of delirium were only 5.7–8.8% among psychiatric morbidity (Huybrechts *et al.*, 2012). In discussing the use of antipsychotics for older people, delirium that is expected to last shortly should be separated from other behavioral and psychological symptoms with dementia.

In another retrospective study including 326 older hospitalized patients with delirium at an acute care community hospital, administration of antipsychotics has been reported not to be associated with increased risk of mortality (Elie *et al.*, 2009). In the present study, which included a much larger number of patients, no patient died because of antipsychotic administration. In the general hospital setting under management by psychiatrists, antipsychotics for delirium would not necessarily cause serious outcome as long as antipsychotic medication lasts only a short period.

There were significant differences in mean age, rate of men, rate of dementia, rate of opioid prescription, rate of hypoactive delirium, and mean maximum dose among the various antipsychotics, suggesting some practice pattern differences for use among the various antipsychotics. Haloperidol was parenterally administered to patients who could not take medicine orally, suggesting that such patients may have been severer in somatic conditions than those with other antipsychotics. The results of higher rate of opioid prescription, higher mean maximum dose, and the worst mean CGI-I score than those of other antipsychotic groups may support that. In patients with olanzapine, higher rate of opioid prescription, higher mean maximum dose, younger age, and lower rate of dementia were observed than others. A long plasma half-life of olanzapine compared with other antipsychotics may have resulted in the choice for such younger patients with severer somatic conditions. In patients with aripiprazole, a higher rate of hypoactive delirium was observed than others. Less sedative property of aripiprazole compared with other antipsychotics may have resulted in the choice for hypoactive delirium (Marder *et al.* 2003). In patients with perospirone, older age and higher rate of dementia were observed than others. A short plasma half-life of perospirone as well as quetiapine compared with other antipsychotics may have resulted in the choice for older demented patients with concerns about the prolongation of a plasma half-life and subsequent disturbance of sleep–wake cycles (Ma *et al.*2007). In patients with quetiapine, lower mean maximum dose and the best mean CGI-I score than others were characteristic, suggesting that quetiapine may have been given patients with simple delirium.

The present study showed that the mean CGI-I score was the level of "much improved", suggesting that effects of antipsychotics on delirium were apparent. So far, effectiveness of antipsychotics on delirium has been reported in some systematic reviews based on experimental studies including a small number of patients (Lacasse *et al.*, 2006; Lonergan *et al.*, 2007). More recently, efficacy and safety of quetiapine for delirium was demonstrated in two randomized, double-blind, placebo-controlled studies, although the numbers of patients in those studies were relatively small (Devlin *et al.*, 2010; Tahir *et al.*, 2010). Thus, evidence about efficacy and safety of antipsychotics in patients with delirium has been accumulating. Our findings of the very low incidence of serious side effects during antipsychotic treatment for delirium in real clinical practice

with a large number of patients support such experimental data, although neither randomized nor placebo-controlled design of this study does not render an opinion about efficacy.

Strengths of this study are a large number of patients with delirium included, availability of causal relationship between adverse events and antipsychotic use due to prospective and close observation by psychiatrists, non-pharmaceutical support, and mirroring real clinical practice. A limitation is non-experimental data so that antipsychotics could not be compared with each other. Another limitation is that the numbers of patients with perospirone, olanzapine, and aripiprazole were relatively small so that the findings about these drugs are not conclusive. Our conclusion can be clearly drawn from a well-designed controlled study, although implementation of a controlled study on delirium treatment in such a large number of patients is challenging.

Conclusions

In the general hospital setting under management including fine dosage adjustment in individual patients and early detection of side effects, antipsychotics might have a low risk in the treatment of patients with delirium, in contrast with antipsychotics for dementia in the nursing home or outpatient settings. A point may be not how to avoid using antipsychotics but how to monitor the risk of antipsychotics once delirium develops.

Conflict of interest

All authors declare that they have no conflict of interest.

Key points

- Out of 2453 patients who received antipsychotics for delirium, 22 had serious adverse events (0.9%), in which aspiration pneumonia, cardiovascular events, and venous thromboembolism were observed.
- Delirium was resolved within 1 week in more than half of the patients.
- In the general hospital setting under management including fine dosage adjustment in individual patients and the early detection of side effects, antipsychotics might have a low risk in the treatment of patients with delirium.

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The predictive value of a change in natural killer cell activity for delirium☆

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ABSTRACT

Purpose: Few studies looking for an effective biomarker to predict delirium have been performed. This study was designed to investigate whether a change in inflammatory status, indicated by blood natural killer (NK) cell activity, predicts delirium.

Methods: This prospective study, performed in 4 university and 1 general hospital from September, 2011 to October, 2012, included 29 patients. Eligible patients were 65–89 years old, newly and emergently admitted. Patients were assessed daily, up to 7 days, for occurrence of DSM-IV-defined delirium. The main outcome measure was change in blood NK cell activity between the first and second mornings after admission.

Results: The mean change in blood NK cell activity on the second morning, compared to the first morning, in patients developing delirium ($n = 9$) was significantly greater than that in patients without delirium ($n = 20$) (6.0% [SD 8.4] vs. −1.4% [9.0], respectively, $t = 2.10$, $P = 0.045$). Significant difference between the groups was still found after adjusting for age, the history of previous delirium, and the Clinical Dementia Rating score ($F = 6.63$, $P = 0.017$). Of note is that 8 of 9 (89%) patients developing delirium had increased blood NK cell activity, as did only 8 of 20 (40%) patients without delirium, giving measurement of this parameter, for distinguishing the two groups, a sensitivity of 89%, specificity 60%, positive predictive value 50%, negative predictive value 92%, positive likelihood ratio 2.22, and negative likelihood ratio 0.19. When combining this predictor with another predictor, a Delirium Rating Scale-Revised-98 severity score of 5 or more at baseline, positive and negative likelihood ratios were 7.80 and 0.24, respectively.

Conclusion: Increase in blood NK cell activity may be associated with developing delirium. Further studies including larger numbers of patients are needed to justify the preventive use of drugs for patients meeting criteria for both predictors.

1. Introduction

Delirium is an acute change in cognition, with altered consciousness and impaired attention, that fluctuates over time (American Psychiatric Association, 2000). Reportedly, its prevalence ranges from 11% to 33% on admission, and its incidence during the hospital stay ranges between 3% and 56% (Michaud et al., 2007). With an increasingly aging population, delirium will increase further. Antipsychotics are widely used for treatment, but the side-effects are a cause for concern. Therefore, there is considerable interest regarding new approaches to the prevention and management of delirium. Although it is challenging to formulate etiopathogenic models that integrate risk factors already identified, it has been suggested that the neuroinflammatory pathway can be a major process underlying delirium when the individual is exposed to an acute systemic inflammatory condition, such as infection or after surgery (Cerejeira et al., 2010). However, studies in humans in this field remain very scarce. Recently, blood levels of interleukin (IL)-6 and IL-8 or the β subunit of the S100 protein were reported to be higher

Abbreviations: CDR, the Clinical Dementia Rating; DRS-R98, the Delirium Rating Scale-Revised-98; IL, interleukin; NK cell, natural killer cell.

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in patients with delirium than in patients without delirium (van Munster et al., 2008, 2010). From a predictive point of view, a biomarker that changes prior to the onset of delirium is required. So far, three of the five studies of insulin-like growth factor 1 (IGF-1) in delirium indicate an association between IGF-1 and delirium occurrence (Adamis and Meagher, 2011). We previously have reported increased IL-1β and decreased natural killer (NK) cell activity with the progress of agitation in patients with Alzheimer disease (Higuchi et al., 2010), and now we have focused on these in the context of delirium prediction. While Adamis et al. (2007) did not recognize a relationship between delirium and blood IL-6, IL-1β or TNF-α, as biological markers, in elderly medical inpatients, the relationship between delirium and blood NK cell activity has not been investigated sufficiently. Due to the swift response of NK cells to inflammation, we hypothesized that a change in blood NK cell activity may predict developing delirium.

2. Methods

We examined the patients included in the DELIRIA-J (Delirium Intervention Research for Improving Acute phase outcomes in Japan) trial, in which preventive effects of ramelteon on delirium were examined (UMIN Clinical Trials Registry ID: UMIN000005591, URL www.umin.ac.jp/ctr/index-j.htm) (Hatta et al., in press); For the purpose of current study, patients assigned to receive placebo ($n = 34$) were included and those assigned to receive ramelteon ($n = 33$) were not, as ramelteon appeared to have preventive effects on delirium.

2.1. Setting and participants

The study proceeded over a 14 month period (September 1, 2011 to October 31, 2012) in 4 university hospitals and 1 general hospital. All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their substitute decision makers.

Eligible patients were 65–89 years old, newly admitted due to an emergency, and able to take medicine orally. Patients were admitted via emergency rooms to intensive care units or regular acute wards. At the time of admission, they were consecutively screened. Patients with delirium at the time of admission were not enrolled in the study. Patients were approached for enrollment purposes before the first night of admission. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 h.

The observation period was one week long, and we supposed that it would be difficult during that time to discriminate between delirium and the cognitive fluctuation of certain diseases, such as severe liver dysfunction and Lewy Body disease. Therefore, such diseases were excluded in advance. Lewy Body disease was excluded on the basis of prior diagnosis.

Withdrawal syndromes of alcohol dependency and drug abuse can include delirium, an etiology obviously different from delirium caused by systemic diseases. Patients with psychotic disorders or bipolar disorders are usually under treatment with antipsychotics, which may prevent the development of delirium. Therefore, such patients were also excluded.

During the study period, 1126 patients were assessed for eligibility, and 1059 patients were excluded. Of the 697 patients admitted to intensive care units, 658 were intubated or had a life expectancy of less than 48 h, and 306 out of 429 patients admitted to regular acute wards had an expected stay of less than 48 h. Diagnoses of severe liver dysfunction, Lewy Body disease, alcohol dependency, psychotic disorder, or bipolar disorder accounted for exclusion of 61 patients. Thus, 1025 patients did not meet inclusion criteria. In addition, 3 patients admitted to intensive care units and 31 patients admitted to regular acute wards refused to participate. Thus, 67 patients, consisting of 24 admitted to intensive care units and 43 admitted to regular acute wards, were included in the study. The 24 patients admitted to intensive care units stayed there for at least the first 3 days, during which blood samples were obtained. Thereafter, 1 patient was transferred to a regular acute ward. The rate of study participation among eligible patients was 66% (67/101). No patient withdrew consent. They were randomly assigned using the sealed envelope method to receive ramelteon (8 mg/day; $n = 33$) and placebo ($n = 34$). The number of patients discharged before day 7 was 13, but there were no discharges within 48 h after admission.

As ramelteon has preventive effects on delirium (Hatta et al., in press), only patients assigned to receive placebo ($n = 34$) were included in the analysis. Delirium developed in 11 patients by day 7 from admission, but not in the remaining 23 patients. Blood samples could not be obtained in 2 patients who developed delirium on the first night. The timing of delirium occurrence in the remaining 9 patients was as follows: the second night, 1 patient; the third night, 4 patients; the fourth night, 1 patient; the fifth night, 1 patient; the sixth night, 2 patients. Also, we failed to obtain blood samples in 3 patients without delirium.

2.2. Assessment and measurement of blood indicators

Before starting the study, site-coordinators were trained as raters to assess outcomes. All site-coordinators were experienced psychiatrists. At the time of admission, baseline characteristics were collected. Also, results of the Acute Physiology and Chronic Health Evaluation (APACHE) II (APACHE II) (Knaus et al., 1985), the Charlson Comorbidity Index (Charlson et al., 1987), and the Eastern Cooperative Oncology Group Performance Status (Falkson et al., 1980) were recorded to indicate physical condition. The Clinical Dementia Rating (CDR) was used to evaluate the existence and severity of dementia (Hughes et al., 1982). A family member who knew the patient before admission was interviewed for the CDR determination. The Delirium Rating Scale-Revised-98 (DRS-R98) was used to measure delirium symptoms (Trzepacz et al., 2010). APACHE II, Performance Status, and DRS-R98 were performed daily up to 7 days. The DRS-R98 was measured between 10:00 and 11:00 AM. Once delirium occurred, the etiology according to the Delirium Etiology Rating Checklist was recorded (Trzepacz, 1999). Delirium was defined according to the Diagnostic and Statistical Manual of Mental Disorder, text revision, 4th ed (American Psychiatric Association, 2000). The same person that diagnosed delirium using the DSM-IV-TR performed the rating scales assessments.

Blood NK cell activity was measured on the first and second mornings after admission. As mentioned in the Introduction, we have previously reported changes in inflammatory markers prior to the onset of agitation in patients with Alzheimer disease (Higuchi et al., 2010). Therefore, we focused on these markers in the context of delirium prediction, and presumed that values of the markers on the second morning would have increased or decreased compared to those on the first morning after admission. Blood samples were obtained by cubital puncture at 6:00 AM before breakfast. NK cell activity was measured in a standard 4 h chromium (Cr) release assay, as previously described (Nakamura et al., 2003). Production of IL-1β from peripheral monocytes was assessed by a high sensitivity enzyme-linked immunosorbent assay (ELISA), as described elsewhere (Baqui et al., 2000). Briefly, after plasma was separated by centrifugation, monocytes were isolated by Ficoll–Hypaque gradient separation followed by overnight plastic adherence. Cultured monocytes were stimulated with LPS of either *P. gingivalis* or *F. nucleatum* for 2, 8, 24, and 48 h, and supernatant fluids were collected. IL-1β levels in supernatant fluids were determined by ELISA.

2.3. Data analysis

We assumed that blood NK cell activity or IL-1β would increase in 50% of patients without delirium and 85% of patients developing delirium, and that 25% of patients would develop delirium. The statistical power was set as power = 1-β = 80%, and sensitivity to $\alpha = 5\%$ to be able to detect differences in the effects of delirium. Power analysis consequently set

the required number of patients at 38 patients without delirium and 13 patients developing delirium. Thus, 51 patients in total were required for the study purpose. We closed study after 67 patients were enrolled (the ramelteon group, $n = 33$; the placebo group, $n = 34$), as 32 patients per group were required for the Deliria-J trial. In the present study, only the placebo group ($n = 34$) was included, which is 67% (34/51) of the required number of patients.

Data were collected on standardized forms and statistical analyses were performed using SPSS version 20-J software (SPSS, Tokyo, Japan). Differences between categorical variables in patient demographics and clinical characteristics were calculated using Fisher's exact test. Differences between sequential variables were calculated using the unpaired t test (with Welch correction if applicable). If data were not sampled from Gaussian distributions, a non-parametric test (Mann–Whitney test) was used. To control for the effect of age, the history of previous delirium, and the CDR score on the change in NK cell activity or IL-1β, one-way analysis of covariance was used. We examined the predictive value of the DRS-R98 severity score at baseline for delirium. Cutoff scores for the DRS-R98 severity scale at baseline were determined using receiver-operator characteristic (ROC) analyses to determine the Youden Index when comparing patients developing delirium with patients without delirium. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (sensitivity/1-specificity), and negative likelihood ratio (1-sensitivity/specificity) were also calculated. All statistical tests were two-tailed. Values of $P < 0.05$ were regarded as statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 shows baseline characteristics. There were no significant differences in the mean age, the rate of previous delirium, the rate of dementia, and the mean CDR score between patients developing delirium and patients without delirium. The numbers of patients with Alzheimer's disease among those developing delirium and those without delirium were 1 (11%) and 2 (10%), respectively. There were no significant differences in admission diagnoses between patients developing delirium and patients without delirium, although stroke, infection, fracture, and heart failure are risk factors for delirium (Michaud et al., 2007).

A total of 5 of 12 patients admitted to ICUs developed delirium, whereas 4 of 17 patients admitted to regular acute wards developed delirium (42% vs. 24%, respectively, relative risk = 1.77, $P = 0.42$).

Table 1
Baseline characteristics.

	Patients without delirium ($n = 20$)	Patients developing delirium ($n = 9$)	P
Age, y	77.2 (6.5)	81.1 (7.5)	0.16
Male, %	6 (30%)	5 (56%)	0.24
Body mass index	21.6 (4.6)	20.9 (3.3)	0.70
Habitual drinking	2 (10%)	1 (11%)	1.00
Habitual sleeping pills	4 (20%)	1 (11%)	1.00
Opioid	0	0	
Previous delirium	0 (0%)	1 (11%)	0.31
Dementia	3 (15%)	3 (33%)	0.34
Alzheimer's disease	2 (10%)	1 (11%)	1.00
Admission diagnosis			
Stroke	3 (15%)	3 (33%)	0.34
Infection	5 (25%)	2 (22%)	1.00
Fracture	5 (25%)	1 (11%)	0.63
Heart failure/myocardial infarction	1 (5%)	2 (22%)	0.22
Other	6 (30%)	1 (11%)	0.38
Number of medical or surgical co-morbidities	1.1 (1.4)	1.1 (1.5)	0.98
Charlson Comorbidity Index	2.5 (2.6)	3.0 (1.7)	0.56
APACHE II	14.6 (2.6)	14.8 (2.6)	0.83
Performance Status	3.3 (0.9)	3.2 (1.0)	0.83
Clinical Dementia Rating	0.4 (0.8)	0.9 (1.0)	0.16
Delirium Rating Scale-Revised-98	3.6 (4.5)	7.4 (4.7)	0.044
Blood NK cell activity on the first morning, %	30.0 (11.2)	33.9 (18.8)	0.49
Blood IL-1β on the first morning, pg/mL	12.4 (6.8)	10.6 (2.0)	0.44

Data represent mean (SD) or n (%), unless otherwise indicated.

3.2. The DRS-R98 severity score at baseline

The mean DRS-R98 severity score of patients developing delirium was significantly higher than that of patients without delirium (7.4 [SD 4.7] vs. 3.6 [4.5], respectively, $P = 0.044$, Table 1). Therefore, we assessed the predictive value of the DRS-R98 severity score at baseline for delirium. Cutoff scores for the DRS-R98 severity score at baseline were determined using receiver-operator characteristic (ROC) analyses to determine the Youden Index when comparing patients developing delirium with patients without delirium.

According to the value of the Youden Index, the best cutoff score for the DRS-R98 severity score at baseline was 4/5. At the score, sensitivity of 78%, specificity 75%, positive predictive value 58%, negative predictive value 88%, positive likelihood ratio 3.12, and negative likelihood ratio 0.29, indicate that the predictive value of the DRS-R98 severity score at baseline for delirium is not so high.

3.3. The CDR score at baseline

We examined if CDR score of 0.5 or more, which indicates coexistence of dementia, predicted the development of delirium. The percentage of patients developing delirium with a CDR score of 0.5 or more at baseline was significantly higher than that of patients without delirium (67% vs. 25%, respectively, relative risk, 2.67, $P = 0.048$). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for use of the parameter for comparison of patients developing delirium with patients without delirium were 67%, 75%, 55%, 83%, 2.67, and 0.44, respectively.

3.4. Change in blood NK cell activity between the first and second mornings after admission

There was no significant difference between the groups in blood NK cell activity on the first morning after admission (Table 1). However, the mean change in blood NK cell activity on the second morning, compared to the first morning, in patients developing delirium was significantly greater than that in patients without delirium (6.0% [SD 8.4] vs. −1.4% [9.0], respectively, $t = 2.10$, $P = 0.045$). Significant difference between the groups was still found after adjusting for age, the history of previous delirium, and the CDR score, which are well-known risk factors of delirium (Litaker et al., 2001) ($F = 6.63$, $P = 0.017$) (Fig. 1). Of note is that 8 of 9 (89%) patients developing delirium had increased blood NK cell activity, as did only 8 of 20 (40%) patients without delirium, giving measurement of this parameter, for distinguishing the two groups, a sensitivity of 89%, specificity 60%, positive predictive value 50%, negative predictive value 92%, positive likelihood ratio 2.22, and negative likelihood ratio 0.19.

3.5. Change in blood IL-1β between the first and second mornings after admission

There was no significant difference between the groups in blood IL-1β on the first morning after admission (Table 1). The significant difference in the mean change in blood IL-1β on the second morning from the first morning between patients developing delirium and patients without

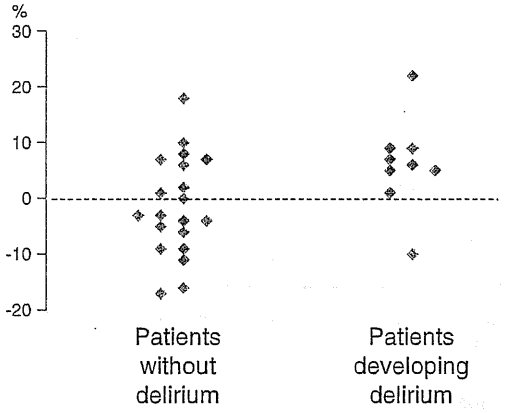

Fig. 1. Change in blood NK cell activity on the second morning compared to the first morning after admission. The mean change in blood NK cell activity on the second morning from the first morning after admission of patients developing delirium was significantly greater than that of patients without delirium after adjusting for age, the history of previous delirium, and the Clinical Dementia Rating score (6.0% [SD 8.4] vs. −1.4% [9.0], respectively, $F = 6.63$, $P = 0.017$). ◆ Cases with the DRS-R98 severity score of 5 or more at baseline, ◆ Cases with the DRS-R98 severity score of 4 or less at baseline.

delirium was not found, either (0.0 pg/mL [SD 0.71] vs. −0.9 pg/mL [2.2], respectively, $t = 1.19$, $P = 0.24$).

3.6. The combination of the DRS-R98 severity score at baseline and the change in NK cell activity

Of particular note is the fact that the percentage of patients developing delirium who had both a DRS-R98 severity score of 5 or more at baseline and an increase in NK cell activity on the second morning compared to the first morning after admission was significantly higher than that of patients without delirium (78% vs. 10%, respectively, relative risk, 7.78, $P = 0.0007$) (Fig. 1). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for use of these two parameters combined for comparison of patients developing delirium with patients without delirium were 78%, 90%, 78%, 90%, 7.80 and 0.24, respectively.

3.7. The combination of the CDR score at baseline and the change in NK cell activity

The percentage of patients developing delirium who had both a CDR score of 0.5 or more at baseline and an increase in NK cell activity on the second morning compared to the first morning after admission was significantly higher than that of patients without delirium (67% vs. 10%, respectively, relative risk, 6.67, $P = 0.0039$). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for use of these two parameters combined for comparison of patients developing delirium with patients without delirium were 67%, 90%, 75%, 86%, 6.67 and 0.37, respectively.

4. Discussion

4.1. Inflammatory response and delirium

An increased inflammatory response has been proposed to be involved in delirium pathophysiology, as have dysfunction of neurotransmitters, decreased oxidative metabolism, abnormal signal transduction, changes in blood-brain barrier permeability, and endocrine abnormalities (Cerejeira et al., 2010). In animal studies, there is compelling evidence that acute peripheral inflammatory stimulation associated with functional and molecular changes in the blood–brain barrier (Sparkman et al., 2006) induces recruitment and infiltration of blood-derived leucocytes into brain tissue (Hofer et al., 2008; Nishioku et al., 2009; Semmler et al., 2005), activation of brain parenchymal cells, and expression of proinflammatory cytokines and inflammatory mediators in the central nervous system (Cerejeira et al., 2010). However, there is inconsistency between findings in clinical studies about blood levels of cytokines and delirium. One has shown higher blood levels of IL-6 and IL-8 in patients with vs. without post-operative delirium (van Munster et al., 2008), but another has shown no relationship between blood IL-6, IL-1β or TNF-α and delirium in elderly medical inpatients (Adamis et al., 2007). Furthermore, there has been little evidence with respect to delirium prediction other than IGF-1 (Adamis and Meagher, 2011). Therefore, the present finding suggesting the association between increasing blood NK cell activity and risk of delirium may be remarkable.

To our knowledge, there is only one previously reported study regarding NK cell activity and delirium, which showed no difference in blood NK cell activity before surgery between 11 patients with postoperative delirium and 15 patients without postoperative delirium (Nakamura et al., 2001). However, blood NK cell activity was measured only once in that study, so whether NK cell activity was ascending or descending was not known. In the current study, blood NK cell activity was measured twice at a 24 h interval, so whether NK cell activity was ascending or descending was determined for each patient.

Although inflammatory blood markers can be abnormal in Alzheimer's disease (Jadidi-Niaragh et al., 2012), the numbers in the current study were only 1 (11%) and 2 (10%) among the patients developing delirium and the patients without delirium, respectively. Therefore, the effect of their inclusion on the present findings may have been small. In addition, inflammatory blood markers in Alzheimer's disease may be more general markers of neurodegeneration without a strong relationship to the more specific behavioral and psychological symptoms of dementia. Such markers may not have affected results of the 2-time-point observation performed at a 24-h interval in this study.

As NK cells can be swiftly mobilized by danger signals and are among the earliest arrivals at target organs of disease (Shi et al., 2011), a change in NK cell activity might be suitable as an early indication of an acute disease such as delirium. In addition, the association between ascending blood NK cell activity and occurrence of delirium demonstrated in this study may support an inflammatory process as an etiology of delirium, as NK cells have been shown to migrate to the inflamed central nervous system (Shi et al., 2011).

Macdonald et al. (2007) reported first that high levels of C-reactive protein (CRP) independently predicted the incidence of delirium, and that a higher initial Mini-Mental State Examination score and low CRP predicted the recovery from delirium at any time during hospitalization for patients with delirium. Since then, attention has been paid to the association between CRP and delirium. Recently, high baseline inflammatory biomarkers such as procalcitonin and CRP reportedly predicted prolonged periods of acute brain dysfunction, implicating inflammation as an important mechanism in the pathophysiology of delirium and coma in mechanically ventilated patients, irrespective of whether patients had sepsis (McGrane et al., 2011). These reports suggest a possible similar mechanism where a general indicator of inflammatory response is associated with delirium.

The present study showed no change in blood IL-1β prior to the onset of delirium. This is consistent with a previous clinical study that showed no relationship between blood IL-6, IL-1β or TNF-α and delirium in elderly medical inpatients (Adamis et al., 2007). Cytokine concentration can vary considerably over time and can be influenced by an individual's genetic background, comorbid systemic inflammatory processes, usage of anti-inflammatory drugs, and exposure to environmental factors (Flirski and Sobow, 2005). Nevertheless, blood IL-1β did not change just before developing delirium, in contrast to development of agitation as a behavioral and psychological symptom of Alzheimer disease, as previously reported (Higuchi et al., 2010; Honma et al., in press). The reason for this difference between delirium and Alzheimer disease is unclear. An explanation may be that blood

IL-1β had not yet been affected just before developing delirium despite increasing blood NK cell activity, as delirium is much more acute-onset than the behavioral and psychological symptoms of dementia (BPSD). Another explanation may be that the etiology of delirium is associated with increasing NK cell activity, but not associated with a change in an inflammatory cytokine such as IL-1β, in contrast to BPSD. Third, a change in blood IL-1β may not necessarily reflect IL-1β levels in the central nervous system.

4.2. Clinical relevance of the change in NK cell activity for delirium prediction

Monitoring patients at risk of delirium for increasing blood NK cell activity more closely may have a mild effect, as the positive likelihood ratio seen in this study was 2.22. In contrast, the negative likelihood ratio, at 0.19, for the change in NK cell activity is moderate for a negative test, and suggests that patients without an increase in NK cell activity are less likely to develop delirium. However, such patients definitely should continue to be monitored regularly, as delirium can actually develop even in these individuals. With respect to the monitoring of patients, therefore, a change in NK cell activity may be of only modest usefulness.

Considering the positive and negative likelihood ratios for comparison of patients developing delirium with patients without delirium, each of two indicators (i.e. the DRS-R98 severity score of 5 or more at baseline and an increase in NK cell activity on the second morning from the first morning after admission) was a mild positive predictor and a mild or moderate negative predictor. However, the combination of these predictors had marked synergistic effects, resulting in a positive likelihood ratio of 7.80 and a negative likelihood ratio of 0.24. These values suggest that the combination of the two indicators is a moderate positive predictor of delirium rather than a negative predictor.

With respect to the predictive value for delirium, the CDR score at baseline was inferior to the DRS-R98 severity score at baseline (positive likelihood ratio: 2.67 vs. 3.12, respectively; negative likelihood ratio: 0.44 vs. 0.29, respectively). Similarly, the combination of the CDR score at baseline and the change in NK cell activity was inferior to the combination of the DRS-R98 severity score at baseline and the change in NK cell activity (positive likelihood ratio: 6.67 vs. 7.80, respectively; negative likelihood ratio: 0.37 vs. 0.24, respectively). However, the difference in the predictive value for delirium between the two parameters was small, and the CDR is simpler than the DRS-R98. Therefore, the combination of the CDR score at baseline and the change in NK cell activity might be worth investigating as well as the combination of the DRS-R98 severity score at baseline and the change in NK cell activity in future studies.

From the perspective of pharmacological delirium prevention, a possibility is raised as the preventive effects of melatonin (Al-Aama et al., 2011) and its analogue ramelteon (Hatta et al., in press) on delirium have been demonstrated in placebo controlled randomized trials. Neither melatonin nor ramelteon has serious side effects, so that their use might not be harmful. Therefore, using melatonin and its analogue might be justified for patients having both the DRS-R98 severity score of 5 or more at baseline and increasing blood NK cell activity, as the combination of both indicators seems to be a moderate positive predictor. Thus, the present findings may lead to a pharmacological strategy for delirium prevention.

4.3. Strength and limitation

One strength of our study was the prospective design. The change in NK cell activity is predictive and is not the baseline measure, which is an important difference from other predictor reports. Another strength was that all participants were emergency cases requiring admission, mirroring real clinical practice. One limitation was that sample size was relatively small. It is possible that the number of patients was too small to detect a sufficiently high positive likelihood ratio or a sufficiently low negative likelihood ratio. Further studies including larger numbers of patients are needed to know if more robust results would be observed.

5. Conclusion

Increased blood NK cell activity is a mild positive predictor of delirium whereas no increased blood NK cell activity is a moderate negative predictor of delirium. The combination of two predictors, a DRS-R98 severity score of 5 or more at baseline and increased NK cell activity, is a moderate positive predictor of delirium. Further studies including larger numbers of patients are needed to justify use of drugs having preventive effects on delirium and no harmful side effects by patients having both predictive criteria prior to developing delirium.

Acknowledgments

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第54回日本老年医学会学術集会記録
〈シンポジウム6：認知症の地域連携〉

4. 地域連携における精神科医療の役割

小田原俊成

Key words：認知症，地域連携，精神科医療，心理・行動症状，権利擁護

（日老医誌　2013；50：205-207）

はじめに

わが国の認知症高齢者は推定300万人を超え，今後も毎年10万人単位での増加が予想されている．本年6月，国の今後の認知症施策の方向性が示され，「ケアの流れ」を脱施設化の方向で推し進め，地域・在宅ケアを基本とする提言がなされた[1]．認知症ケアには身体症状のみならず，心理・行動症状（behavioural and psychological symptoms of dementia；BPSD）への対応や，住環境，生活背景，尊厳に対する配慮，さらには介護者に対する支援など包括的対応が求められ，精神医学的対応の重要性が指摘されている．本稿では，昨年11月に報告された厚労省の「新たな地域精神保健医療体制の構築に向けた検討チーム第2Rとりまとめ」に記された今後の認知症と精神科医療のあり方（厚生労働省，2011[2]）に関する提言の中で，精神科医療に関する要諦について解説し，専門医療機関としての著者らの施設における認知症高齢者に対する取組を紹介する．

地域精神保健医療体制における認知症患者に対する精神科医療の役割[2]

①地域での生活を支えるための精神科医療

・専門医療機関による早期の診断

専門医療機関（主として認知症疾患医療センター，以下センター）の整備の必要性が数値目標とともに掲げられた．また，診断後の支援体制（かかりつけ医への紹介，サービス支援調整など）の構築や多職種との連携強化の主導的役割がセンターに期待されている．

・経過や状態像に応じた診療と生活のアドバイス

・家族や介護者への相談支援や訪問支援

早期の鑑別診断によって将来の症状や経過を予測し，BPSDの発生予防に役立つような生活面のアドバイスを行う役割が期待されている．また，医療機関連携のほか，地域包括センター，介護サービス事業所，ケアマネージャーなど，多職種との連携による相談・訪問支援体制の強化が謳われている．

・施設等で生活する認知症高齢者への訪問支援

・精神症状で緊急を要する認知症患者への24時間対応体制

・精神科作業療法や重度認知症デイケアの提供

精神科医療機関の訪問診療や訪問看護機能の推進，訪問支援および救急外来機能（ソフト救急）の充実による在宅でのBPSD対応支援体制の構築，退院後の療養の継続性の観点から作業療法や重度認知症デイケアなど，多様な外来医療提供体制の充実が謳われている．外来機能の充実とともに，必要に応じて救急入院対応可能な医療機関との連携体制の構築が不可欠である．

②BPSDを有する患者への精神科医療

・BPSDへの適切な治療

・BPSDを伴う認知症患者への円滑な医療の提供（地域連携）

BPSD発現予防のアドバイスを行い，発現した場合には生活歴や生活状況を考慮し環境調整を行った上，必要最低限の薬物療法を行うことを推奨している．入院治療を要する場合でも，短期間で退院につなげるため，精神保健福祉士等の地域連携担当者や，受け皿となる地域の介護支援専門員，各種施設の支援相談員などとの連携推進を謳っている．また，連携強化を目的として退院支援・地域連携クリニカルパスの活用を勧めている．

③身体疾患を有する認知症患者への入院医療

・合併症の状態像に応じた精神病床の受け入れ先―総合病院精神科と精神科病院の役割分担―

Role of psychiatric care in regional collaboration on dementia

Toshinari Odawara：横浜市立大学附属市民総合医療センター精神医療センター

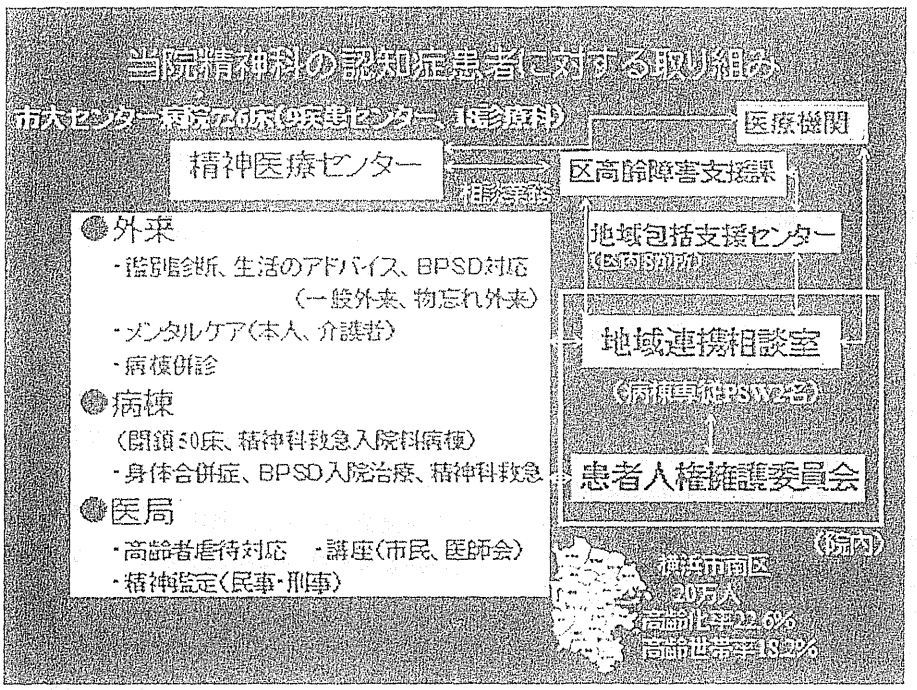

図1　当院精神科の認知症高齢者に対する取り組み

表1　精神医療センター高齢入院患者症例における認知症群の臨床的特徴

	認知症群（105例）	非認知症群（213例）
平均年齢	74.6±6.8歳*	71.7±6.1歳
在院日数	48.9±29.8日	63.2±35.4日*
非自発入院（%）	75.1*	57.3
隔離（%）	44.0*	24.3
拘束（%）	37.2*	16.4
自宅退院（%）	24.7	60.3*

認知症群は非自発入院，行動制限を要する割合が高く，自宅退院率が低かった．
認知症群の在院日数は非認知症群と比べ，短かった．

急性疾患の治療では，他の専門診療科とリエゾン可能な総合病院精神科を有する医療機関またはセンター，慢性疾患の治療には精神科病院と，疾患や状態像に応じた入院受け入れ先の役割分担を求めている．他の専門診療科をもたない精神科医療機関が多いことから，対診を利用した医療機関間の連携推進の必要性についても触れている．

当院の取り組み

当院では，図1に示すような枠組みで認知症診療の地域連携を行っている．外来，病棟，医局（院内）に分け，認知症高齢者に対する取り組みを紹介する．

①外来

鑑別診断は主として専門外来（もの忘れ外来）で行い，BPSD対応，生活面のアドバイス，本人・介護者のメンタルケアは一般外来でも行っている．平成22年4月～23年6月の精神センター65歳以上高齢外来患者510例中，精神医学的診断でF0群（認知症，MCIおよびせん妄などの器質性精神障害）の占める割合は47.8%と最も多く，紹介理由としては認知症の鑑別診断が47.4%と最多であった．

②病棟併診

総合病院精神科における重要なコンサルテーション業務の一つとして，せん妄への対応があげられる．院内併診における65歳以上高齢者の精神医学的診断分類はやはりF0群が最も多く（60%以上），併診理由としてはせん妄やBPSDへの対応が約9割とほとんどを占めていた．

③入院

平成18～23年の65歳以上高齢入院患者318例を，認知症群（BPSDおよび身体合併症併存例）と非認知症群に分けて臨床的特徴の比較を行った（表1）．認知症群は非自発入院，行動制限（隔離，身体拘束）を要する割合が高かった．認知症群では入院同意能力が不十分であり，治療行為に対する協力が得られにくいことが示された．認知症群の在院日数は非認知症群と比べて短かく，自宅退院率は低かった．当院の認知群は治療後に施設や

他院へ転院することが多く，BPSDや身体疾患を有する認知症患者の在宅介護の困難さの一端を示している．認知症疾患治療病棟における入院長期化が問題となっているが，退院促進のためには在宅医療・介護や社会資源の充実など包括的な支援体制の強化が必要であろう．また，平成23年に治療目的で入院した認知症患者54人中，約2割にあたる11人に入院中身体疾患が併発した．呼吸器・尿路感染症や転倒による骨折を抜いて，深部静脈血栓症が最も多く（5人）認められた．当院入院の認知症患者は，高齢，向精神薬使用，身体疾患の併存のほか，身体拘束を用いる頻度が高く，精神科領域で使用される深部静脈血栓症ガイドラインの高リスク群に該当する症例がほとんどである．その他，当院は精神科救急基幹病院として精神科3次救急症例の受け入れを行っているが，BPSDを理由とした認知症の措置入院症例が散見される．認知症患者は身体疾患の管理が不十分であることが多く，BPSDの治療とともに身体管理や環境調を並行して行う必要がある．

④医局

近年，高齢者虐待防止法の施行により，認知症高齢者に対する人権擁護の意識が高まりつつある．児童虐待症例に比べ，高齢者虐待例に対する認知度は低い状況だが，外傷事例やBPSD対応事例の中に，虐待事例が散見されることがあり，疑い事例では，随時院内で人権擁護委員会を開催し，主治医，精神科医，看護師，ケースワーカー，行政職，ケアマネージャーなど多職種による検討を行い，対応を行っている．また，複雑な背景を有する民事鑑定（成年後見鑑定）とともに，刑事鑑定（窃盗，傷害など）の依頼もあり，人権擁護の観点から精神科医の重要な職分となっている．

おわりに

増加し続ける認知症高齢者が安心して生活できる社会の実現には，当時者および介護者に対する心身両面のケアが重要である．地域ケア推進のため，精神科医療機関は介護や福祉との連携，地域住民への啓発活動，当事者の人権擁護に積極的な機能を果たしていく必要がある．

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II. 高齢者によくみられる精神症状の鑑別診断と治療

カタトニア

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Catatonia in the elderly

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Abstract

Catatonia is a syndrome characterized by mutism, stupor, immobility, negativism, posturing, stereotypy, and echophenomena. Not only patients with schizophrenia, but also patients with general medical disease, mood disorder, and substance-related disorder exhibit catatonia. In the patients with catatonia, it is recommended to examine whether they have a general medical disease. We present two catatonic elder patients. Case 1 exhibited catatonia with vascular dementia, and was revealed to have anti-phospholipid antibody syndrome. Case 2 exhibited catatonia with dementia with Lewy bodies, and was revealed to have Hashimoto's encephalopathy.

The first recommended treatment for catatonia is benzodiazepines. In case of benzodiazepine resistance or malignant catatonia, it should be considered electroconvulsive therapy, but it needs to be carefully implemented for elder patients.

Key words: catatonia, organic catatonic disorder, geriatric psychiatry

はじめに

カタトニアは，無言症(mutism)，昏迷(stupor)，無動(immobility)，拒絶症(negativism)，姿勢保持(posturing)，常同症(stereotypy)，反響現象(echophenomena)などを特徴とした，気分，情動，認知の障害と深く関連した特定の運動異常症候群である．

1874年Kahlbaumは，代表的著作である‘緊張病(Die Katatonie oder das Spannungsirresein)’[1]の中で，26人のカタトニア自験例を記載し，カタトニアが，筋強剛，無言，拒絶，カタレプシーといった症状から始まり，続いて常同症，興奮という過活動状態が出現し，進行性の経過をとること，そして，カタトニアを呈していた期間には，不安症状，抑うつ症状，精神病症状を生じていたことが後に想起されることが特徴であると報告した．これらの症例は，カタトニアの原因疾患としては，現在のDSM-IV診断では双極性障害，うつ病性障害，統合失調症，せん妄に分類され，なかには腹膜炎，結核，進行麻痺といった身体疾患に関連したものも含まれていた[2]．

Kraepelinは，カタトニアが慢性的に経過し，

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最終的に精神荒廃に至るという経過に注目し，カタトニアを早発性認知症の一亜系として規定した．この考えはDSMやICDに引き継がれており，現在もこれらの診断基準では，カタトニアは統合失調症の一亜型として規定されている[3]．しかし，Abramsら[4]は，カタトニア症状を呈した55例を検討し，統合失調症の診断は4例のみであり，34例で躁病，5例でうつ病の診断基準を満たしたと報告している．また他の9例では，てんかん，中毒性精神病，脳炎，アルコール性認知症，薬剤誘発性精神病といった脳器質性疾患を有していたと報告している．この報告から，カタトニアを，統合失調症に限らず，気分障害や脳器質性疾患にも多くみられる一定の症候を呈する症候群としてとらえる考えが広まっており，カタトニアは高齢者診療においても遭遇することのある症候群である．

本稿では，高齢者のカタトニアの診断，分類，原因，治療について解説する．

1. カタトニアの診断・分類

DSM-IV-TRでは，緊張型統合失調症295.20について，①カタレプシーまたは昏迷として示される無動症，②過度の運動過活動(無目的で外的刺激に影響されないもの)，③極度の拒絶症(明らかに動機のない抵抗，あるいは動かそうとする試みに対する硬直した姿勢の保持)あるいは無言症，④姿勢，常同運動，顕著な衒奇症，顕著なしかめ面などとして示される自発運動の奇妙さ，⑤反響言語または反響動作を挙げており，これらの中から少なくとも2つが優勢である臨床像をもつものを緊張型の統合失調症と診断するとしている．また，気分障害においても，'緊張病性の特徴を伴うもの'として，該当する場合は特定することとなっている．そのほか，一般身体疾患によるカタトニアは，293.89という分類番号が割り振られている．

Finkらは，DSMのカタトニア診断について，無動と興奮が非特異的症状であること，症状の持続時間が規定されていないこと，姿勢に関する項目の重複があることといった問題点を指摘し，カタトニアの診断基準として以下のような基準を提唱している[3]．

A. 無動，無言，昏迷が少なくとも1時間持続し，以下の症状を少なくとも1つ以上伴う：カタレプシー，命令自動，姿勢常同(2回以上観察または誘発されること)．

B. 無動，無言，昏迷がない場合，以下の症状を少なくとも2つ以上，2回以上観察または誘発される：常同症，反響現象，カタレプシー，命令自動，姿勢常同，拒絶症，両価性．

カタトニア症状は，barbiturateやbenzodiazepineによって軽快することが知られており，少量のベンゾジアゼピン系薬物を投与し，反応性から診断するという方法も知られている．

カタトニアには，幾つかの亜型が存在することが知られている．

(1) 制止カタトニア(retarded form of catatonia)は，Kahlbaum症候群ともいわれており，患者は，反応に乏しく，昏迷状態にある．また，無言症，拒絶症，姿勢常同，筋強剛を示す．通常良性で，予後良好といわれている．

(2) 興奮カタトニア(excited form of catatonia)は，興奮，滅裂な発語・行動，落ち着きのなさ，錯乱，脱衣，自傷行為，強い恐怖感，作話，不眠，見当識障害などを呈し，多くは数時間から数日で発症する．発熱，心拍上昇，高血圧，頻呼吸といった自律神経症状を呈することも多い．無言症は目立たないが，悲観的，常同行動，しかめ面，姿勢保持，反響言語，反響動作といったカタトニア症状を有していることから，詳細な診察によって診断される．

(3) 悪性カタトニア(malignant catatonia: MC)は，急性発症，発熱，自律神経症状(異常血圧，頻脈，頻呼吸)を呈する．しばしば予後不良で致死的な経過をとることも多い．悪性症候群(neuroleptic malignant syndrome: NMS)と臨床的な特徴，経過，治療反応性が似ていることから，悪性カタトニアとの鑑別は困難であるとされている．MC/NMSでは，クレアチンキナーゼの上昇や血清鉄の低下がみられるという報告もある．

2. カタトニアの原因疾患

ここでは，著者らが経験した高齢者のカタトニアの症例を報告し，カタトニアの診断について考察する．

[症例1] 89歳女性，抗リン脂質抗体症候群と脳血管性認知症に伴うカタトニア

既往歴：高血圧，狭心症，脊柱管狭窄症．

現病歴：X−4年ころより内服薬を飲み忘れたり，料理の味付けを失敗したりすることがあった．近医の物忘れ外来を受診し，改訂版長谷川式認知機能スケール(HDS-R)で，26/30と軽度認知機能障害レベルと判断されていた．X年1月より，家に閉じ込められている，監視されている，といった被害妄想が出現．その後，拒食，全裸で外出しようとする，壁に頭を打ちつけようとするなど，行動がまとまらなくなり，X年2月上旬に精神科病院認知症病棟に入院となった．

入院後経過：入院時は，しかめ面で全く喋ろうとせず，食事も拒否していた．被害妄想や拒否が強く，詳細な認知機能評価や画像評価が困難であった．輸液を行い，点滴にてhaloperidol 2.5 mgを一度投与した．その後，看護師を気遣う発言がみられるなど，少し落ち着いて話をするようになった．しかし，haloperidol投与後3日目より，パーキンソニズムが出現した．その2日後から，無言症，姿勢常同，筋強剛を認め，カタトニアとなった．flunitrazepam 1 mgを点滴投与したところ，30分ほどで筋緊張は改善し，疎通性も良好になった．しかし，数時間すると，再び同様の状態になるため，身体疾患の精査目的で横浜市立大学附属病院へ転院となった．

転院後の身体診察では，左上肢に局所的な著しい浮腫を認めた．血液検査では，血小板13.4万/μL(18-39万/μL)，CRP 10.23 mg/dL(<0.2 mg/dL)，D-dimer 8.7 μg/mL(<1.0 μg/mL)と異常値を認めた．そのほか，各種ウイルス検査，感染症検査などで，異常所見は認めなかった．膠原病の検索では，抗核抗体homogeneous 40倍(<40倍)，抗カルジオリピン抗体26 U/mL(<10 U/mL)が検出された．髄液検査は異常なかった．全身CT検査では，異常所見は得られなかった．頭部MRI検査では，びまん性の脳萎縮を認め，左後頭葉に陳旧性の脳梗塞を認め，大脳深部白質に全般性に虚血性病変を認めた．脳波検査では，基礎律動の徐波化を認めていた．

臨床症状とベンゾジアゼピン系薬物への反応性から，カタトニアと診断した．身体疾患としては，抗リン脂質抗体症候群が挙げられ，これによる静脈炎，脳血管性認知症と考えられた．また，抗精神病薬の投与がカタトニアを誘発した可能性も考えられた．

治療としては，まずは，抗精神病薬の中止と，十分な量の輸液を行った．また，抗リン脂質抗体症候群に対しては，warfarin投与を行った．徐々に，筋強剛，姿勢常同は軽快し，拒否や妄想も消失し，穏やかに食事摂取ができるようになった．2週間ほどで血小板，CRP，D-dimerなどの血液検査所見も正常化した．入院1カ月で大学病院を退院した．

[症例2] 73歳女性，レビー小体型認知症(dementia with Lewy bodies: DLB)と慢性型橋本脳症の合併によるカタトニア

既往歴：高血圧，Basedow病，下部胆管狭窄症．

現病歴：60歳頃より，意欲がなくなり，自宅の片付けなどもせず，生活がだらしなくなっていった．X−1年12月頃から，'天井に虫が見える'といった幻視が出現し，X年3月に，精神科受診となった．受診時，短期記憶障害を中心に認知機能障害を認め，HDS-Rは18/30，mini mental state examination(MMSE)は22/30と認知症レベルであった．パーキンソニズムは認めなかった．血液検査では，一般検査，微量元素，膠原病検査，甲状腺ホルモン値は正常範囲内であった．抗甲状腺抗体(抗サイロペルオキシダーゼ抗体55.4 U/mL(<0.3 U/mL)，抗サイログロブリン抗体>100 U/mL(<0.3 U/mL))がそれぞれ高値であった．頭部MRI検査では，海馬の萎縮や白質病変を認めていた．頭部SPECT検査では，後頭葉の血流は保たれていた．パーキンソニズムがないこと，頭部SPECT検査の所

見，そのほか嗅覚障害，便秘症，レム睡眠行動障害といったDLBを示唆する症状に乏しかったが，認知機能障害に幻視が合併していたことからレビー小体型認知症の可能性(possible DLB)を考えた．自己免疫性脳症の一つである慢性型橋本脳症の合併が疑われたが，高齢であることから，家族と相談のうえで，免疫療法は行わず経過を観察することとなった．X年6月下旬に，自宅で全く動けなくなったため，救急車で横浜市立大学附属病院を受診し，緊急で入院となった．

入院時，表情は固く，発語は認めなかった．筋固縮が著しく，姿勢常同を認め，カタトニアと考えられた．一般血液検査は，異常値を認めなかった．髄液検査で，タンパクが41 mg/dLとごくわずかに上昇を認めた．脳波検査では，全般性に徐波の混入が目立っていた．頭部MRI検査は変化なかった．抗精神病薬の中止と，十分な輸液を行い，もともとの経過から慢性型橋本脳症が疑われていたため，ステロイドパルス療法(methylprednisolone 1,000 mg 3日間)を開始した．その後，速やかに疎通性，表情，動作が改善し，虫の幻視の訴えも消失した．1週間後に認知機能評価を行ったところ，HDS-R 23/30，MMSE 26/30と，認知機能も改善を認めた．髄液タンパクも低下しており，DLBと慢性型橋本脳症の合併に伴ってカタトニアを生じていたと考えられた．

その後，3年ほど，外来で経過を観察しているが，カタトニア症状を呈することはない．夫が腰痛で動けないときには，介護をすることもあり，現在も夫婦での生活を続けている．

カタトニアの原因疾患は多岐にわたるが，身体疾患に伴うカタトニアの頻度は比較的報告が多い．Takataら[5]は，71例の高齢者のカタトニアを報告し，その内訳として20例が一般身体疾患に伴うもの，19例が気分障害，10例が統合失調症やそのほかの精神病，10例が向精神薬誘発性のもの，7例がアルコールなどの薬物関連のもの，4例が不安障害，1例が特定不能のものだった．表1に，カタトニアを起こすことのある原因疾患を挙げたが，多岐にわたり，いずれもカタトニア症状だけから原因疾患を特定することは困難である．カタトニアに遭遇したときには，ここで挙げた症例のように，身体疾患を考え，詳細な診察とともに，血液検査，頭部画像検査，脳波検査，髄液検査を行い，致死性または重篤な後遺症を残す可能性のある疾患を除外することが重要である．

症例1は，脳血管性認知症と，抗精神病薬の投与後に，カタトニアを呈した症例であったが，背景として抗リン脂質抗体症候群の関与が考えられた．本症例は，カタトニア症状のほか，上肢の浮腫と血小板数の低下，D-dimerの上昇から，抗カルジオリピン抗体測定を行い，抗リン脂質抗体症候群の診断に至った．本症例と同様に，Cardinalら[6]も，精神病症状とカタトニアが初発症状だった抗リン脂質抗体症候群を報告しており，抗凝固療法と免疫抑制療法を行っている．抗精神病薬の中止と輸液だけでなく，warfarinによる抗リン脂質抗体症候群に対する治療もカタトニアに対して効果的であったと推察される．

症例2は，possible DLBと慢性型橋本脳症の合併によるカタトニアの症例であった．橋本脳症は，抗甲状腺自己抗体陽性者において精神神経症状を呈する自己免疫性脳炎である．脳炎に関連するカタトニアの報告は多い[7]．本症例は，甲状腺自己抗体があるものの，possible DLBとして経過観察されていたという経過があり，カタトニアが出現してから早期に橋本脳症が疑われステロイド治療が行われた．ステロイドパルス療法後に，カタトニアと認知機能障害の改善が速やかにみられたことからは，これらの症状がともに橋本脳症に関連していたことを示唆していると考えられた．

2症例とも精査により身体疾患の診断に至ったが，1例目は脳血管性認知症を呈しており，2例目は，DLBが疑われていた．もともと認知機能障害を呈していたという経過からは，認知症の進行，または，認知症に伴うカタトニアと診断されるかもしれない．しかし，Swartzら[8]は3例の高齢のカタトニアの症例を報告し，いずれ

表1　カタトニアの原因疾患

神経疾患	悪性症候群，後シナプス性ドーパミン受容体遮断薬の投与，ロラゼパムその他鎮静剤の離脱，無動筋強剛症候群(akinetic-rigid syndrome)，右頭頂葉領域のくも膜嚢胞，星状膠細胞腫，聴覚疾患，小脳性カタレプシー，脳血管疾患(脳底動脈血栓症，側頭葉の両側出血，大脳出血・梗塞，皮質静脈血栓症，くも膜下出血，硬膜下血腫など)，橋中心髄鞘崩壊，皮質基底核変性症，ジストニア，脳炎(ヘルペス，トリパノソーマ・クルージ)，脳症(HIV，ウェルニッケ脳症，ライム病ボレリア)，自己免疫性脳炎(辺縁系脳炎，橋本脳症)，脳底動脈切開に伴う線維筋異形成症，ロボトミー，頭部外傷，ハンチントン舞踏病，水頭症，出産後出血による下垂体機能不全，特発性反復性昏迷，遺伝性神経代謝性疾患，Locked-in症候群，結核性髄膜炎，脳髄膜炎，多発性硬化症，神経梅毒，非痙攣性てんかん重積，淡蒼球ルイ体萎縮症，パーキンソニズム，レビー小体型認知症，脳血管性認知症，前頭葉側頭葉萎縮症，脳炎後パーキンソニズム，進行性多巣性白質脳症，進行性核上性麻痺，裂脳，複雑部分発作，スティックマン症候群，小脳腫瘍摘出後，テイサックス病，側頭葉てんかん，結節硬化症，腫瘍(視床下核中脳腫瘍，脳梁，第三脳室膠細胞腫，脳室上びまん性松果体腫)，植物状態，エコノモ脳炎，ウィルソン病
精神疾患	急性ストレス障害，神経性無食欲症，自閉性障害，緊張病を伴う短期反応性精神障害，解離性障害，大うつ病(緊張病症状を伴うエピソード)，気分障害，悪性症候群，PTSD，統合失調症，物質使用(3,4メチレンジオキシメタンフェタミン，アルコール，アンフェタミン，フェンシクリジン，鎮静剤離脱)
心理的要因	移民，失恋，外国訪問
身体疾患	エイズ，急性間欠性ポルフィリン症，アジソン病，細菌性敗血症，気管支漏，カルチノイド腫瘍，糖尿病性ケトアシドーシス，脳症(肝性，HIV関連，ウェルニッケなど)，不明熱，熱射病，肝不全，遺伝性コプロポルフィリン症，ホモシスチン尿症，高カルシウム血症，低ナトリウム血症，副甲状腺機能亢進症，甲状腺機能亢進症，低体温症，腸アトニー，マラリア，悪性症候群，中毒(一酸化炭素，四エチル鉛)，物質使用(アルコール，ジスルフィラム，有機フッ素化合物，フェンシクリジン)，腎不全，SIADH，梅毒，SLE，温熱損傷，血栓性血小板減少性紫斑病，結核，腸チフス，尿毒症

(文献[14]より改変)

も，重度認知症と誤診されていたという．認知症が一番に疑われても，可能な範囲で身体疾患の除外を行うことが必要である．

3. カタトニアの治療

カタトニアの治療について，身体疾患が特定される場合は，その原疾患の治療が優先されることはいうまでもない．しかし，カタトニアによって血栓症，廃用症候群，誤嚥，窒息，低栄養からの全身状態の悪化などを引き起こすことがあるため，実際は，身体疾患の精査・加療とともに，カタトニア症状に対しての加療も並行して行われる．

カタトニアに対する薬物療法に関しては，第一選択薬としては，ベンゾジアゼピン系薬物が推奨されている．Northoffら[9]によると，頭部SPECT検査を用いた研究で，カタトニア患者では，左大脳においてGABA$_A$受容体の結合能の減少がみられたとも報告されている．海外では，カタトニアを診察した場合，ベンゾジアゼピンチャレンジテストとして，lorazepam 1mgの静注を行い，5分後に診察，質問を行う．5分後に反応がなかった場合は，更にもう1mg静注する．良好な反応は通常10分以内に起こるとされている．diazepamに換算する場合は，1回投与は5mgとされている．反応がみられない場合は，3時間ごとに再度同様のテストを行う．ベンゾジアゼピンチャレンジテストに反応がみられる場合には，反応が得られた量のベンゾジアゼピン系薬物を継続し，その間に原疾患の加療を行う．高齢者への投与や過鎮静を呈している場合は，適宜減量が必要である．また，治療に反応して患者が動けるようになった場合，転倒することがあるため，高齢者や歩行障害のある患者では，注意が必要である[10]．

抗精神病薬の投与については，第一選択薬と

しては使わないという考えが多い．カタトニア患者に，抗精神病薬を投与した場合，NMSの発症率は3.6％と報告されており，これは，抗精神病薬が投与されるすべての一般患者におけるNMSの発症率0.07-1.8％と比較して有意に高く，抗精神病薬の投与には注意が必要である[10]．NMSの発症予測については，十分なエビデンスはないものの，抗精神病薬投与後にNMSを発症したカタトニア患者は，抗精神病薬投与前の血清鉄の値が低いということが報告されている[11]．

ベンゾジアゼピン系薬物の反応が悪い場合や，効果が限られている場合，また，MC/NMSを呈している場合には，電気痙攣療法が検討される．Suzukiら[12]は，45歳以上の緊張病型統合失調症患者11例に対して電気痙攣療法を行ったところ，すべての症例で速やかな改善が得られたものの，1年後には，63.6％が再発したと報告している．また，慢性の神経疾患では電気痙攣療法の治療反応性が低下することが指摘されている[13]．高齢者においては，認知症を合併していることが多いことからも，電気痙攣療法の適応は，慎重に検討される必要がある．

おわりに

カタトニアについて，診断，分類，原因疾患，治療について概説した．カタトニアを呈する高齢者を診療した際は，速やかに診断し，身体疾患の除外を行い，カタトニアの治療を開始することが重要である．

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特集―せん妄の診断と治療の現在Ⅱ

せん妄時の身体合併症と事故防止のために

岡村　泰*　金子　友子**　小田原俊成***

抄録：総合病院における入院患者において，せん妄は11～33％と高頻度にみられる病態であり，合併により入院期間や死亡率の増加につながることから，せん妄対応は医療機関の重要な課題となっている。せん妄に併発しやすい外傷（事故）として転倒・転落が挙げられるが，院内転倒症例に併存する疾患の頻度としては認知症に次いで多い（院内転倒症例の６％）ことが報告されており，事故防止の観点からも対策が必要である。せん妄の危険因子として，年齢（高齢），疾患の重症度，認知機能障害，脳卒中，代謝・電解質・内分泌異常，感染症，薬物の離脱が報告されており，こうした要因の把握と適切な予防措置および早期発見，早期治療が転倒・転落などの事故防止につながることが期待される。本稿では，当院におけるせん妄と転倒・転落に関する調査および転倒・転落防止に対する取り組みを紹介する。せん妄時の身体拘束の是非に関しては，点滴やカテーテル類の身体的治療を併行して行う必要がある場合や，自身や他人に危険を及ぼす可能性が高い場合は，医療スタッフ，本人，周囲の者でよく協議した上で必要最小限の拘束の適応が事故防止の観点から重要と思われる。せん妄のような意識障害を有する患者には同意能力に問題があると考えられるが，インフォームド・コンセントが必要ないと安易に考えるべきではなく，入院時および定期的に患者の同意能力の判定を行い，インフォームド・コンセントを得る努力を行うべきである。　精神科治療学　28(9)；1129-1136，2013

Key words：*delirium, risk factor, comorbidity, injury, fall*

はじめに

入院中の患者にせん妄が生じることにより，入院期間や入院中の死亡率の増加[9]，術後せん妄による術後合併症の増加[23]，高齢者では退院後の死亡率や施設入所，認知症発症率の増加[26]といった医療・ケアに関する諸問題が報告されてきた。また，入院期間や入院中死亡率の増加には，転倒・転落事故との関連が指摘されている[4]。このように，せん妄は合併症や事故の併発により，患者の生命予後，機能予後に多大な影響を与える病態であり，その対応には医療従事者・家族や介護サービス等の多大な人的資源を要する。

総合病院におけるせん妄の入院時有病率は11～33％，入院中の発症率は３～56％で[17]，65歳以上

Accident prevention for patients with delirium.

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の高齢者の術後せん妄の発症率はさらに高く，15～53％と言われている[10]。また，院内転倒症例に併存する疾患の頻度としては，せん妄は６％と認知症に次いで多いことが報告されており[4]，せん妄に伴う転倒は日常診療において，しばしば遭遇する事故と言える。せん妄の30～40％は予防可能であるという報告[10]や，せん妄や転倒の予防に関する介入プログラムがせん妄や転倒の減少に寄与したという報告も散見されており，医療従事者はせん妄や転倒・転落について十分認識し，適切な対応をとる意識をもつことが事故防止の観点から重要である。しかし，せん妄の診断率は低く，８割以上の患者で不適切な対応がとられ[12]，転倒に関する問診を行うのはプライマリケア医の約37％にすぎないという指摘もある[13]。

本稿では，特にせん妄時の身体合併症と事故防止の観点から，前半では，せん妄時に併発しやすい身体疾患（せん妄の危険因子）やせん妄時に併発しやすい外傷について，後半ではせん妄患者の事故防止に対する自施設での取り組みを含めて解説する。また法律的な問題についても言及する。

Ⅰ．せん妄時に併発しやすい身体疾患について
―せん妄の危険因子―

個々の症例におけるせん妄の危険因子の把握は，せん妄の予防，早期発見，早期治療，事故防止の観点から重要である。せん妄の危険因子は，①準備因子（せん妄の発症の基盤となる素因的因子），②直接因子（せん妄の発症に直接関与していると考えられる因子），③促進因子（せん妄の促進，増悪に関与する因子）に分けられる[17]。Michaudらは，成人のせん妄包括的ガイドラインを作成するために，過去のガイドライン，系統的レビュー，ランダム化比較試験，コホート研究を網羅的に検索・評価し，中でも質の高い文献を多職種による専門家組織により，根拠に基づき集学的手法で評価した。推奨度はエビデンスレベルにより，高い順に３段階（A，B，C）に分類した（表１）。ここでは，推奨度Ａにあたるせん妄の危険因子について概説する。

1．高齢者（70歳以上）
年齢とともに身体機能は低下し，高齢者ではせん妄のリスクが高くなる。さらに，高齢者が急性の疾病や外傷により入院した場合，せん妄，転倒，機能低下，合併症等の危険性が高くなり，施設入所や死亡率の増加，医療費の増加につながることが指摘されている[11]。したがって，高齢者の入院治療においては，せん妄の発症予防，早期治療介入が重要である。

2．疾患の重症度
疾患の重症度はせん妄の危険因子である[20]。ICUに入院した高齢者のせん妄発生率は70～87％と言われている[10]。また，進行がん患者入院時の26～44％にせん妄が生じ，死に至る数日～数時間は80％以上がせん妄に至ることが報告されている[5]。ICU入室を要する手術後の患者や救急患者や進行性の担がん患者等の重症患者の診療においては，原疾患の治療はもちろんのこと，環境への配慮を含めたせん妄の予防的措置をあらかじめ講じておくことが重要である。

3．認知機能障害
認知機能障害はせん妄の危険因子の中でも特に重要である。例えば，非心臓手術の術後せん妄の最大の危険因子は認知機能障害と向精神薬とする系統的レビュー[8]や，高齢者の術後せん妄と最も関連する因子は年齢と認知症[24]とする文献がある。入院の段階で，病歴聴取と問診により認知機能低下が疑われる場合，Mini Mental State Examination（MMSE）や改訂長谷川式簡易知能評価スケール（HDS-R）などを用い，認知機能を評価しておくことが推奨される。しかし，緊急入院や併存疾患が重症な症例では，認知機能の評価が困難な場合もあるので，家族等から入院前の認知機能や生活機能について確認しておくことが重要であろう。また，高齢者でせん妄が遷延する場合，認知症の可能性を念頭に置き，治療にあたるべきであろう。

4．脳卒中
脳卒中患者の26％にせん妄が出現し[7]，発症後