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Original Article

Fasting Blood Interleukin-1β and Interleukin-6 Levels as Predictors of Agitation in Patients with Alzheimer's Disease

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SUMMARY

Background: The increased prevalence of Alzheimer's disease (AD) represents an important public health issue in most countries worldwide. Interleukin-1β (IL-1β) and IL-6, which are inflammatory cytokines, are involved in the pathogenesis of AD; however, their role in agitation associated with AD remains unclear. To assess the accuracy of blood IL-1β and IL-6 as predictors of agitation in patients with AD, we examined the relationship between the levels of these interleukins and the appearance of agitation.

Methods: We used the clinical dementia rating (CDR) scale as an indicator of the severity of dementia as well as blood IL-1β and IL-6 levels in the morning and evening in 40 elderly patients who were institutionalized in an elderly nursing home. We followed up these patients and evaluated agitation using the modified overt aggression scale (MOAS) for one year.

Results: MOAS results indicated that the initial values for CDR as well as IL-1β and IL-6 levels in the morning and IL-1β levels in the evening were significantly higher in patients with a high MOAS score than in those with a low score. A multiple logistic regression analysis revealed that CDR values and IL-1β and IL-6 levels in the morning significantly contributed to a higher MOAS.

Conclusion: The results showing higher IL-1β and IL-6 levels in the morning prior to the appearance of agitation in AD patients confirm the role of these interleukins in agitation, and suggest that they are useful predictors of agitation in these patients.

1. Introduction

Alzheimer's disease (AD) has a negative impact on not only the cranial nerve symptoms of cognition and emotion, but also the activities of daily life and physical symptoms. The dysfunctions accompanying AD become the primary reason for institutionalization in elderly nursing homes. As society ages, the prevalence of AD will increase. Recent increases in the prevalence of AD represent a social issue; it has reached more than 40% in individuals older than 85 years and the percentage of AD patients among those with dementia in the U.S. was reported to be 75–80%.[1,2] Previous studies showed that microglial cells, which are nerve immunocompetent cells, were activated with the accumulation of neurotic plaques (amyloid β aggregates), that nerve fiber disorders (tau protein aggregates) were an important pathological condition of AD,[3] and that hyperinsulinemia, hypertension, hyperlipidemia, and the ApoE gene were closely associated with the onset of AD.[4,5]

Interleukin-1β (IL-1β), an inflammatory cytokine, is functionally related to AD.[6] Higuchi et al. reported that IL-1β levels were elevated in AD patients with agitation.[7] Furthermore, elevated IL-1β and IL-6 levels with agitation were found to significantly contribute to the later onset of AD.[8] However, the relationship between IL-6 levels and the pathological condition of AD remains controversial.[9] Moreover, it has not yet been established whether changes in the levels of cytokines, including IL-1β and IL-6, are the cause or result of agitation in AD patients.[10] Therefore, markers that predict agitation in AD patients need to be identified.

The pathological mechanisms responsible for agitation in AD patients may be elucidated,[9] and when the relationship between these cytokines and the development of agitation is clarified, the prediction of agitation in these patients will be important for controlling AD symptoms.[11,12] In the present study, the relationship between IL-1β and IL-6 levels and the subsequent appearance of agitation in AD patients was investigated to elucidate their involvement in agitation associated with AD.

2. Subjects and methods

2.1. Subjects

Forty patients with AD (aged 78.2 ± 6.77 years (mean ± SD), 15 men and 25 women) who were institutionalized in an elderly nursing home in Fukushima prefecture in Japan between 2005 and 2010

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were selected as subjects. At baseline, each subject provided written informed consent or each contributor of subjects submitted written representative informed consent. The present study was approved by the Ethical Committees of Kanazawa University Graduate School of Medical Science and the elderly nursing home that co-operated with this study, and adhered to the ethical guidelines of the Declaration of Helsinki.

2.2. Clinical evaluation

Patients underwent a uniformed structured clinical evaluation with a medical history, neurological examination, neuropsychological performance testing, including the Mini-Mental State Examination,[13] and a standard clinical assessment, including a brain scan. A consensus diagnostic process established or ruled out the diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; the presence of probable or possible AD was assessed according to the National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association criteria;[14] and the stage of dementia was evaluated according to the Clinical Dementia Rating Scale.[15] Based on the results obtained, there were 25 mild (CDR 1), 10 moderate (CDR 2), and 5 severe (CDR 3) AD patients. A psychiatrist (K. H.) and geriatrician (I. M.), experts in the diagnosis and evaluation of the conditions of the elderly, including patients with dementia, assessed the diagnosis of AD and subsequent symptoms of agitation every month for 1 year. None of the subjects had any chronic inflammatory diseases, such as rheumatoid arthritis, hepatitis, malignant diseases, respiratory diseases, urinary tract diseases, or infectious diseases. None of the subjects took non-steroidal anti-inflammatory drugs (NSAIDs), steroids, or drugs for agitation or sleep. No subjects were lost to the follow-up during the study period.

2.3. Measurement of IL-1β and IL-6 levels and assessment of agitation

To obtain baseline data on IL-1β and IL-6 levels, blood was drawn by cubital puncture at 6:00 under fasting conditions and at 18:00 on the next day when patients were at rest, and inflammation was not present soon after patients had been institutionalized in the elderly nursing home. The Modified Overt Aggression Scale (MOAS)[16] was used to assess agitation and scores were continuously obtained for 1 year after the observation period had been initiated. The relationship between MOAS scores and baseline IL-1β or IL-6 levels was examined.

2.4. Production of IL-1β and IL-6 from peripheral monocytes

The production of IL-1β and IL-6 from peripheral monocytes was evaluated using a highly sensitive enzyme-linked immunosorbent assay (ELISA).[17] Briefly, after plasma had been separated by centrifugation, monocytes were isolated by Ficoll-Hypaque gradient separation followed by plastic adherence overnight. Cultured monocytes were stimulated with *Porphyromonas gingivalis* or *Fusobacterium nucleatum* as lipopolysaccharide (LPS) for 2, 8, 24, and 48 hr and supernatants were collected. IL-1β and IL-6 levels in supernatants were measured by ELISA.

2.5. Statistical analysis

Baseline IL-1β and IL-6 levels in the morning or evening were analyzed using a one-way analysis of variance (ANOVA) among 3 groups that were divided according to the severity of dementia (CDR), and Dunnett's test was used for multiple comparisons between the values obtained for CDR 1 and CDR 2 or 3. In the analysis of the relationship between baseline IL-1β or IL-6 levels in the morning or evening and subsequent MOAS scores, CDR scores and IL-1β or IL-6 levels in the morning or evening were compared using the Student's *t*-test after MOAS had been divided into 2 groups (high MOAS group (≤ 8; agitation group) and low MOAS group (> 8; non-agitation group)). A multiple logistic regression analysis was conducted using an agitated state as an observatory variable and sex, age, CDR scores, and IL-1β and IL-6 levels in the morning or evening as explanatory variables to identify predictors of agitation in AD. All statistical analyses were performed using two-tailed tests and p-values less than 5% were considered to be significant.

3. Results

Table 1 shows the sex ratio, age, and IL-1β and IL-6 levels in the morning and evening in each CDR group. Although no significant differences were observed in the sex ratio or age among each CDR score group, significant differences in IL-1β levels in the morning and evening were noted among each CDR group using the one-way ANOVA. Dunnett's multiple comparison test showed that IL-6 levels in the moderate AD group in the morning and IL-1β levels in the moderate and severe groups in the evening were significantly higher than those in the mild group.

Comparisons of the sex ratio, age, CDR scores, and IL-1β and IL-6 levels in the morning and evening between the high and low MOAS groups are shown in Table 2. CDR scores and IL-1β (morning and evening) and IL-6 (morning) levels were significantly higher in the agitation group than in the non-agitation group.

Since CDR scores were significantly higher in the agitation group than in the non-agitation group, a multiple logistic regression analysis was conducted using CDR scores, the sex ratio, age, and IL-1β and IL-6 levels in the morning as explanatory variables and agitation and non-agitation as objective variables (Table 3). Factors that significantly contributed to agitation were IL-1β and IL-6 levels in the morning, but not CDR scores. A multiple logistic regression analysis

Table 1
Initial blood IL-1β and IL-6 levels in the morning and evening in each CDR group.

CDR (score)	Number of subjects	Sex (male vs. female)	Value(Mean ± SD)				
			Age (years)	IL-1β (morning)* (pg/ml)	IL-6 (morning)* (pg/ml)	IL-1β (evening)** (pg/ml)	IL-6 (evening) (pg/ml)
1	25	9:16	78.7 ± 6.63	23.9 ± 6.21	41.6 ± 10.84	18.0 ± 6.93	35.7 ± 9.89
2	10	4:6	77.8 ± 7.73	29.4 ± 7.92	53.8 ± 14.60*	26.7 ± 12.04*	45.6 ± 15.22
3	5	2:3	76.2 ± 6.42	31.0 ± 7.21	40.8 ± 13.22	29.2 ± 7.33*	32.8 ± 14.06

CDR score 1, mild; 2, moderate; 3, severe.
Significant differences in mean values among the three CDR groups revealed by a one-way ANOVA, followed by the post hoc Dunnett test's; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ significantly different from that in CDR 1.

Table 2
Initial blood IL-1β and IL-6 levels and CDR scores by MOAS at the endpoint.

MOAS (score)	Number of subjects	Sex (male vs. female)	Value(Mean ± SD)					
			Age (years)	CDR (score)	IL-1β (morning) (pg/ml)	IL-6 (morning) (pg/ml)	IL-1β (evening) (pg/ml)	IL-6 (evening) (pg/ml)
Low (< 8)	25	9:16	78.7 ± 6.68	1.20 ± 0.577	23.2 ± 5.68	40.5 ± 11.55	18.3 ± 7.09	35.7 ± 9.89
High (≥ 8)	15	6:9	77.3 ± 7.06	2.00 ± 0.655***	31.1 ± 6.97***	51.3 ± 12.74**	27.1 ± 10.7**	41.3 ± 15.63

MOAS, modified Overt Aggression Scale.
Significant differences in mean values between subjects with higher MOAS and those with a lower MOAS score of less than 8 points by the Student's *t*-test; * p < 0.05, ** p < 0.01, *** p < 0.001.

Table 3
Multiple logistic regression analysis of the subsequent appearance of agitation using initial blood IL-1β and IL-6 levels in the morning.

Variables	Regression coefficient (SE)	Odds ratio (95% CI)	p value
Sex (male vs. female)	-0.166 (1.27)	0.847 (0.071–10.1)	0.896
Age (years)	-0.035 (0.095)	0.966 (0.802–1.16)	0.715
CDR (score)	1.44 (0.670)	4.23 (1.14–15.8)	0.031
IL-1β (morning) (pg/ml)	0.212 (0.098)	1.237 (1.021–1.50)	0.030
IL-6 (morning) (pg/ml)	0.082 (0.041)	1.085 (1.002–1.18)	0.046

MOAS, modified Overt Aggression Scale; CDR, clinical dementia rating.

Table 4
Multiple logistic regression analysis of the subsequent appearance of agitation using initial blood IL-1β and IL-6 levels in the evening.

Variables	Regression coefficient (SE)	Odds ratio (95% CI)	p value
Sex (male vs. female)	-0.300 (1.07)	0.741 (0.090–6.08)	0.780
Age (years)	-0.022 (0.077)	0.979 (0.841–1.14)	0.779
CDR (score)	1.43 (0.648)	4.194 (1.179–14.92)	0.027
IL-1β (evening) (pg/ml)	0.071 (0.051)	1.074 (0.971–1.19)	0.166
IL-6 (evening) (pg/ml)	0.041 (0.034)	1.042 (0.975–1.11)	0.229

MOAS, modified Overt Aggression Scale; CDR, clinical dementia rating.

using IL-1β and IL-6 levels in the evening instead of IL-1β and IL-6 levels in the morning as explanatory variables identified CDR scores, but not IL-1β and IL-6 levels in the evening, as a factor that significantly contributed to agitation (Table 4).

4. Discussion

Approximately 50% of patients with dementia who were institutionalized at nursing homes have been reported to exhibit agitation.[18–20] In the present study, high IL-1β and IL-6 levels were identified as predictors of agitation in AD patients. Higuchi et al. reported an increase in IL-1β levels at the agitation stage in AD patients.[7] In contrast, Adamis et al. did not observe any relationship between blood IL-6, IL-1β, or TNF-α levels and delirium in elderly medical inpatients;[21] however, their cohort study did not focus on AD patients only as subjects. Previous studies reported a functional relationship between IL-1β levels and AD.[6] Elevated IL-1β levels in the cerebral fluid and blood of AD patients were also noted in a case-control study.[22] Systemic inflammatory markers are associated with an increased risk of AD.[23] AD patients were more likely to develop delirium after systemic infection, and the negative relationship between the progression of AD and inflammatory responses was identified as the mechanism responsible for greater deteriorations in the cognitive status before the progression of AD during this period.[24] The administration of NSAIDs has been shown to suppress the development and symptoms of AD.[25] Bauer et al. showed that increased blood levels of cytokines, such as IL-1β, were accompanied by systemic responses to infectious diseases.[26] The present result showing that high IL-1β levels at rest in AD patients were associated with later agitation is consistent with the findings of Bauer et al. In addition to previous findings showing that inflammatory cytokines play an important role in depression, epidemiological and neuropathological data demonstrated that inflammatory processes were activated in the brains of AD patients.[27] Based on accumulated knowledge, the present result showing elevated IL-1β levels in the pre-agitation stage (low MOAS) of AD patients suggests that inflammation induced by excitatory cytokines, including IL-1β, contribute to the exacerbation of agitation in AD.

In the present study, a relationship was observed between not only IL-1β levels and agitation in AD patients, but also IL-6 levels. However, in contrast to IL-1β, the relationship between IL-6 levels and agitation in AD patients remains controversial.[9] A previous study demonstrated that IL-6 levels in the cerebral fluid of AD patients were increased,[28] whereas other studies reported that they were decreased[29] or remained unchanged.[30] Similarly, the relationship between blood IL-6 levels and agitation in AD patients remains unclear.[31,32] Zuliani et al. showed that the relationship between plasma IL-6 levels and the onset of AD in the late stage disappeared after adjustments for risk factors for other circulatory diseases.[33] The measurement point of cytokine levels, i.e. the circadian cycle of AD patients described below, has been suggested as a cause of these differences.[9] In other cases, these differences may be observed because patients with inflammatory diseases or those using NSAIDs were not excluded as controls of AD.[34] The present results are of significance because patients with inflammatory diseases and those using NSAIDs were excluded as subjects and cytokine levels were measured in the morning and evening. Previous studies reported that IL-6 functions as a mediator in the relationship between inflammation and AD, similar to IL-1β.[35,36]

In the present study, IL-1β and IL-6 levels were measured not only under fasting conditions in the morning, but also in the evening. Based on previous findings,[37–39] the present results suggest that agitation in AD patients is closely related to a disorder in the circadian cycle, including sleep-wakefulness patterns,[37] because the ratio of night-time activity was higher in AD patients than in healthy subjects[38] and circadian cycles in AD patients were weakened in the non-agitation stage, similar to the agitation stage.[39] Therefore, further studies are needed to investigate the relationship between the circadian cycles of IL-1β and IL-6 and subsequent agitation in AD patients. As a result, the relationship between the IL-1β and IL-6 levels and the agitation was less significant in the evening than that in the early morning. This may be explained by the presence of patients without differences in these cytokine levels between the early morning and evening. Disorders in the circadian cycles of IL-1β and IL-6 may be associated with the subsequent appearance of agitation in AD patients; however, the present results do not strongly support this relationship. Further studies using an evaluation method that accurately assesses circadian cycles are needed to elucidate this

relationship in more detail.

A long-term longitudinal study with a large sample size that examines changes in blood markers after the amelioration of agitation is also needed to clarify the causal relationship between IL-1β levels, IL-6 levels, or inflammation and the onset or exacerbation of agitation in AD. Further studies are also warranted to establish whether agitation itself occurs during inflammatory processes in not only AD, but also other diseases associated with dementia.

There are some limitations that need to be addressed. The sample number was very small. Although comparisons were conducted among each CDR group, there was no control group. Therefore, further studies using larger sample numbers and a control group are needed to confirm the results obtained in the present study.

5. Conclusion

Increases in IL-1β and IL-6 levels were observed before the appearance of agitation in AD patients, and fasting blood IL-1β and IL-6 levels in the early morning have potential as predictors of agitation. The present results suggest that IL-1β and IL-6 are involved in the appearance of agitation in AD patients.

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Conflicts of interest

K. H. has received lecture honoraria for Dainippon-Sumitomo, Eisai, Janssen, Meiji Seika, MSD, Otsuka, Takeda, and Tanabe-Mitsubishi, and has served as a consultant for Dainippon-Sumitomo, MSD, and Meiji Seika within the past 24 months. The other authors declare no conflicts of interest.

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