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Cytokines and acute phase response in delirium☆,☆☆

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Abstract

Objective: This study aimed to examine the expression patterns of pro- and anti-inflammatory cytokines in elderly patients with and without delirium who were acutely admitted to the hospital. **Methods:** All consecutive patients aged 65 years and older, who were acutely admitted to the Department of Internal Medicine of the Academic Medical Center, Amsterdam, a tertiary university teaching hospital, were invited. Members of the geriatric consultation team completed a multidisciplinary evaluation for all study participants within 48 h after admission, including cognitive and functional examination by validated measures of delirium, memory, and executive function. C-reactive protein and cytokines (IL-1β, IL-6, TNF-α, IL-8, and IL-10) were determined within 3 days after admission. **Results:** In total, 185 patients were included; mean age was 79 years; 42% were male; and 34.6% developed delirium within 48 h after admission. Compared to patients without delirium, patients with delirium were older and had experienced preexistent cognitive impairment more often. In patients with delirium, significantly more IL-6 levels (53% vs. 31%) and IL-8 levels (45% vs. 22%) were above the detection limit as compared with patients who did not have delirium. After adjusting for infection, age, and cognitive impairment, these differences were still significant. **Conclusions:** Proinflammatory cytokines may contribute to the pathogenesis of delirium in acutely admitted elderly patients.

Keywords: Delirium; Cytokines; Elderly; Hospital admission; Immunology

Introduction

Infections in humans are characterized by local, systemic, and central nervous system (CNS) effects. The effects of inflammation and infection on the aging brain are highly complex. The mechanisms, however, that mediate the behavioral effects of peripherally released cytokines on the brain, often described as sickness behavior, have partly been elucidated over the past decade [1–4].

Cytokines, a diverse group of peptide molecules that regulate cell and tissue functions, are responsible for sickness behavior including malaise, fatigue, and reduced appetite. These cytokines, mainly interleukin-1 (IL-1α and IL-1β), IL-6, and tumor necrosis factor (TNF)-α, are supposed to act on the brain via a fast neural pathway and a slower humoral pathway [5]. The proinflammatory IL-1 is able to induce its own synthesis and the synthesis of other cytokines that potentiate (e.g., TNF-α, IL-6, and IL-8) or antagonize its effect (IL-10). Proinflammatory cytokines are involved in the production of IL-1 in the brain [4–6], and peripheral and central administration of IL-1β in animal studies induced all components of sickness behavior [7]. In humans, a high-serum IL-6 and other cytokines have been associated with neuropsychiatric illness like cognitive decline in dementia [8] and in depression [9] and cognitive impairment and fatigue in cancer [10,11].

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☆☆ S.R. is the principal investigator of the study; she designed the protocol, supervised its progress, and was involved in the acquisition of the data. B.M. was involved in the planning of the study and the acquisition of the data. J.K. was responsible for the statistical analysis. S.R., B.M., J.K., and M.L. drafted the manuscript. All authors contributed to the interpretation of the data and to the revisions of the paper; all read and approved the final manuscript.

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Delirium, an acute neuropsychiatric syndrome, characterized by deranged consciousness and by cognitive and attentional disturbances with a typical fluctuating course, is also hypothesized to be induced by circulating cytokines [12,13]. Although a variety of factors are associated with delirium, such as psychiatric illness, older age, and cerebral vascular disease, the pathophysiology of delirium remains poorly understood. Interestingly, delirium has been recognized as a frequent manifestation of infections in the elderly [14]. Delirium usually disappears once the underlying illness that causes delirium has been resolved and is a fully reversible phenomenon [15] similar to cytokine-induced sickness behavior. Moreover, animal studies have demonstrated that cytokines can cause a reduction in the acetylcholinergic pathways [16], which are supposed to be impaired in delirium [17]. Based on this information, delirium may be considered as a distinct part of sickness behavior that can be seen as the outward expression of a potentially reversible episode of brain inflammation and is triggered by peripheral immune stimulation [12,13,18,19]. These and other studies resulted in several hypotheses [13,20,21], suggesting that cytokines may be involved in the pathogenesis of delirium. There are, however, no data on the association between peripheral cytokine levels and delirium.

Aim

We performed a study among consecutive elderly patients who were acutely admitted to the hospital to compare the expression patterns of pro- and anti-inflammatory cytokines in patients with and without delirium.

Methods

Patients

All consecutive patients aged 65 years or older, who were acutely admitted to the Department of Medicine of the Academic Medical Center, Amsterdam, a 1024-bed university teaching hospital, were invited. Patients were excluded from the study if they were unable to speak or understand Dutch or English, if they or their relatives did not give permission to participate in the study, if they came from or were transferred to another ward, or if they left the ward within 48 h. Before enrolment, informed consent was obtained from the patient or substitute decision maker. The hospital's medical ethics committee approved the study.

Procedures

Members of the team completed a multidisciplinary evaluation for all study participants within 48 h after admission. The team was composed of a geriatric physician, a fellow in geriatric medicine, and research nurses trained in geriatric medicine. Demographic and clinical data were collected. The reason for admission was collected and expressed in *International Classifications of Diseases* code. Five cytokines, namely, IL-1β, IL-6, IL-8, IL-10, and TNF-α, and C-reactive protein, as a marker of the acute phase response, were measured in a blood sample taken in the morning within 3 days after admission. The blood samples were centrifuged, and serum was stored at −80°C until determination. Cytokine concentrations (TNF-α, IL-1β, IL-6, IL-8, and IL-10) were measured using a cytometric bead array immunoassay (BD Biosciences Pharmingen, San Diego, CA, USA). Considering the dilutions at which the samples were tested, actual detection limits (DLs) were as follows: 2.5 pg/ml for TNF-α, 80 pg/ml for IL-1β, 10 pg/ml for IL-6, 20 pg/ml for IL-8, and 10 pg/ml for IL-10.

Measurement instruments

Within 48 h after admission, research nurses interviewed patients as well as medical and nursing staff. At the time of hospital admission, cognitive impairment was recorded by two validated instruments [Mini Mental State Examination (MMSE) and Informant Questionnaire on Cognitive Decline (IQCODE)]. The MMSE is the internationally most widely used bedside screening instrument for detection of general cognitive impairment in the elderly [22]. The MMSE measures cognitive functioning on a scale of 0 (*poor*) to 30 (*excellent*), wherein a score of less than 24 indicates cognitive impairment and a score of 30 simply means that the person's general cognition is not impaired due to dementia or delirium. The IQCODE assesses the possible presence of dementia before hospital admission based on the response of an informant who had known the patient for at least 10 years and could assess any decline in memory or cognition [23,24]. The informant was asked to recollect the situation 2 weeks before the illness leading to the hospital admission and to compare it with the situation 10 years before. The score is the average of the 16-item scores, each rated from 1 (*much improved*) to 5 (*much worse*). Patients with a mean score of 3.9 or more were considered to have serious cognitive impairment. Final classification for having premorbid cognitive impairment was based on an earlier diagnosis of dementia or on the MMSE score for patients without delirium, whereas for patients with delirium, the combination of both instruments (MMSE and IQCODE) was applied if no earlier diagnosis of cognitive impairment was available. In case of conflicting outcome, the score of the IQCODE was used.

The physician scored the presence of delirium within 48 h after admission using the Confusion Assessment Method (CAM). The CAM is a structured interview of delirium symptoms based on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria. This instrument has been found to be reliable, sensitive, and specific [25]; a valid Dutch version was available [26].

Functionality was measured by the modified KATZ-ADL Scale, a 15-item scale developed for use in a geriatric population [27]. The KATZ-ADL consists of one scale for patients and one for their relative or informant. The KATZ-ADL as scored by the relative was used, and once more, the relative/informant was asked to recall the situation before admission.

Statistical analysis

Data were analyzed using SPSS-PC software version 11.5. Rating scale data were expressed as median scores and quartiles because of their distribution. Differences in baseline characteristics were tested using chi-square tests or the Mann–Whitney *U* test.

We have performed a multivariate analysis to identify whether disturbed cytokine levels were associated with delirium after adjustment of the well-known risk factors for delirium, that is, age, cognitive impairment, and infection. We created a variable that indicates whether the cytokine level was above DL or not (1, if the value was above the limit; 0, if the value was below the limit). We combined this value with the measured cytokine level containing the true value for the patients with a cytokine concentration above DL; otherwise it was 0. Combining both variables into the analysis determines both the association of having a cytokine level below or above the DL and whether the cytokine concentration itself is associated with delirium. A *P* value of <.05 was considered statistically significant.

Table 1
Baseline characteristics of acutely admitted elderly patients with and without a prevalent delirium after acute admission

	Delirium	No delirium	*P* value
Number of patients	64	121	
Age (years)	81.2 (7.1)	77.3 (8.0)	.002
Gender (% male)	34	45	.16
Cognitive impaired (%)	62	20	<.001
Functional impairment [number of (I)ADL disabilities]* (%)			
0 limitations	6.3	21.3	
1–3 limitations	8.3	29.2	
4–6 limitations	14.6	13.5	
7 or more limitations	70.8	36.0	<.001
Admission reason (%)			
Infectious disease	48	41	
Malignancy	9	12	
Disease of digestive system	8	15	
Water and electrolyte disturbances	16	7	
Cardiovascular diseases	8	9	
Other	11	15	.33
CRP (mg/l)			
% Below DL	6	9	.53
Median (IQR)	72.5 (30.5–185.0)	87.0 (33.0–170.0)	.83
TNF-α (pg/ml)			
% Below DL	89	88	.77
Median (IQR)	4.8 (2.8–10.0)	3.1 (2.8–5.4)	.68
IL-1β (pg/ml)			
% Below DL	98	99	.64
Median (IQR)	–	–	
IL-6 (pg/ml)			
% Below DL	47	69	.04
Median (IQR)	21.1 (12.9–39.2)	19.9 (12.9–30.6)	.88
IL-8 (pg/ml)			
% Below DL	55	78	
Median (IQR)	53.8 (30.9–79.1)	40.3 (27.9–559.8)	.83
IL-10 (pg/ml)			
% Below DL	94	96	.52
Median (IQR)	13.8 (10.8–20.6)	20.3 (15.8–29.2)	.29

* 29% missing.

Table 2
Factors associated with delirium in a multivariate logistic regression analysis

Variable	Odds ratio (95% CI)	*P* value
IL-6		
IL-6 concentration	1.00 (0.99–1.01)	.962
IL-6 below DL	2.39 (1.03–5.56)	.044*
Age	1.02 (0.97–1.07)	.534
Cognitive impairment	7.87 (3.56–17.40)	<.001*
Infection	1.29 (0.60–2.75)	.514
IL-8		
IL-8 concentration	1.00 (0.99–1.00)	.60
IL-8 below DL	2.57 (1.06–6.26)	.038*
Age	1.03 (0.98–1.09)	.231
Cognitive impairment	7.22 (3.25–16.04)	<.001*
Infection	1.15 (0.533–2.46)	.729

* 29% missing.

Results

During the inclusion period, 576 patients aged 65 years and older were admitted. Of these patients, 88 came from another ward, resulting in 488 eligible patients. One hundred eighty-two patients were not included because no informed consent was provided, because the patients were unable to speak or understand Dutch or English, or because they were discharged within 48 h. In total, 306 patients were included; due to financial and time limitations of our experienced laboratory analyst, a random sample of 185 patients was taken for the current study. Nonselected and selected patients' data regarding mean age, the male/female ratio, and the frequency of patients with delirium were similar. Baseline characteristics of the 185 patients with and without delirium are presented in Table 1. Mean age was 80 years; 42% were male; and 64 patients (34.6%) were diagnosed with delirium. Patients with delirium were significantly older, had (preexisting) cognitive impairment more often, and were more impaired in daily activities compared to patients without delirium. The vast majority had C-reactive protein levels above the DL; these levels showed no significant difference between patients with and without delirium (*P*=.83). Nearly all patients had TNF-α, IL-1β, and IL-10 levels below the DL (88%, 99%, and 96% respectively). Significantly more nondelirious patients had IL-6 levels below the DL (69%) compared with delirious

patients (47%; *P*=.04). A similar finding was seen for IL-8: more nondelirious patients had IL-8 levels below the DL (78% vs. 55%; *P*=.001). Limiting the analyses to the serum concentrations above the DL, we observed no significant difference between delirious and nondelirious patients for IL-6 or IL-8.

After adjusting for age, cognitive impairment, and infection as possible confounders for delirium, having an IL-6 level above the DL of 10 pg/ml was significantly associated with delirium [OR=2.4 (1.0 to 5.6)]. We could not observe an independent association of the actual level of IL-6 (Table 2). A similar independent association between IL-8 and delirium was found; having an IL-8 level above the DL of 20 pg/ml was significantly associated with delirium [OR=2.6 (1.1 to 6.3)], and no association of the actual IL-8 concentration was observed. No independent association between IL-10, TNF-α, or CRP and delirium was found.

Discussion

In this sample of consecutive, acutely hospitalized elderly patients, 34.6% met the criteria for delirium. Patients with delirium had significantly less often IL-6 and IL-8 levels below the DL. These differences remained after adjusting for age, preexisting cognitive impairment, and hospital admission due to infectious disease.

This is the first study that shows a relationship between peripherally measured cytokine levels and delirium as a symptom/exponent of sickness behavior in acutely admitted elderly. This finding is in line with some previous other observations. One study investigated the relationship between low-baseline insulin growth factor (IGF)-1 and delirium in acutely hospitalized elderly subjects [28]. IGF-1 is known as a neuroprotective cytokine, which inhibits cytotoxic cytokines. From the results of this study, it was concluded that below a certain level of IGF-1, the brain is vulnerable to cytotoxic effects of circulating cytokines, generated by an acute illness and presenting with delirium.

Furthermore, it was shown that cognitive function can be impaired by a systemic infection in patients with a neurodegenerative disorder such as Alzheimer's disease and that this cognitive decline is preceded by raised serum levels of IL-1β [29]. In longitudinal, population-based studies, increased serum levels of IL-6 were also associated with cognitive decline [30–32], but any pathophysiological relationship [contribution to cognitive decline or consequence of (early) dementia] remains unclear. In our population, some patients with delirium also had IL-6 levels below the DL. Interestingly, in otherwise apparently healthy brains, cytokines may have no delirious effect, but when neuronal damage is present, such as in dementia, as well as in cerebrovascular disease or even as a result of aging of the brain [33], some cytokines may enhance neurodegenerative processes, which leads to the syndrome of delirium, perhaps even irrespective of their circulating cytokine levels.

Theories and, later on, findings indicate that the pathophysiology of delirium is a consequence of imbalances of several neurotransmitter systems, resulting in reduced synthesis of acetylcholine in the brain [33–36]. Peripheral signals activating central pathways is not easy to understand because cytokines are large lipophobic proteins or peptides that do not easily cross the blood–brain barrier. Nevertheless, a recent study showed a temporarily elevation of IL-6 in the cerebrospinal fluid after cardiac surgery [37]. Many hypotheses regarding the blood-borne cytokines' passage through this barrier have been proposed. One of which could be its binding to the cerebral vascular endothelium [19]. Neuropathological studies have shown that systemic inflammation causes activation of vascular endothelial cells and perivascular cells [38].

One limitation of this study could be the number of patients with detectable levels of cytokines; nevertheless, we decided not to give undetectable levels the level of the DL. The number of missing KATZ scores obtained from the family is also a limitation. We decided not to use the combined KATZ score of patients and caregivers; instead, we only used that of the caregivers. Consequently, we had too few scores for the MVA. Another limitation is the moment of obtaining blood samples: the vast majority was taken within 3 days after admission. Another limitation of our study is that the cytokines are measured in peripherally obtained blood and, therefore, do not necessarily reflect the local pathophysiological process in the brain during delirium. However, it is well established that the release of proinflammatory cytokines IL-1β, IL-6, and TNF-α is supposed to induce a typical pattern of behavior response, which has been collectively referred to as sickness behavior [7,39]. The amounts of cytokines are normally high during acute infections in patients showing sickness behavior [40], but there is growing evidence that low circulating levels of inflammatory cytokines may also influence the CNS [39]. Whether this is the case in delirium is not yet clear, but it might explain why delirium was present in some patients with cytokine levels below DL.

It can be concluded that more research is necessary to study the possibility that inflammatory mechanisms are involved in pathogenetic pathways of delirium. The present study suggested a role for proinflammatory cytokines in delirium, independent of infectious diseases.

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References

[1] Crestani F, Seguy F, Dantzer R. Behavioural effects of peripherally injected interleukin-1: role of prostaglandins. Brain Res 1991; 542:330–5.

[2] Konsman JP, Blond D, Vigues S. Neurobiology of interleukin-1 receptors: getting the message. Eur Cytokine Netw 2000;11: 699–702.

[3] Dantzer R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur J Pharmacol 2004;500:399–411.

[4] Dantzer R, Konsman JP, Bluthe RM, et al. Neural and humoral pathways of communication from the immune system to the brain: parallel or convergent? Auton Neurosci 2000;85:60–5.

[5] Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;5:154–9.

[6] Dantzer R, Bluthe RM, Laye S, et al. Cytokines and sickness behavior. Ann N Y Acad Sci 1998;1840:586–90.

[7] Anforth HR, Bluthe RM, Bristow A, et al. Biological activity and brain actions of recombinant rat interleukin-1alpha and interleukin-1beta. Eur Cytokine Netw 1998;9:279–88.

[8] Kalman J, Juhasz A, Laird G, et al. Serum interleukin-6 levels correlate with the severity of dementia in Down syndrome and in Alzheimer's disease. Acta Neurol Scand 1997;96:236–40.

[9] Kahl KG, Bens S, Ziegler K, et al. Cortisol, the cortisol–dehydroepiandrosterone ratio, and pro-inflammatory cytokines in patients with current major depressive disorder comorbid with borderline personality disorder. Biol Psychiatry 2006;59:667–71.

[10] Meyers CA. Mood and cognitive disorders in cancer patients receiving cytokine therapy. Adv Exp Med Biol 1999;461:75–81.

[11] Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 2005;104:788–93.

[12] Eikelenboom P, Hoogendijk WJ, Jonker C, et al. Immunological mechanisms and the spectrum of psychiatric syndromes in Alzheimer's disease. J Psychiatr Res 2002;36:269–80.

[13] Stefano GB, Bilfinger TV, Fricchione GL. The immune-neuro-link and the macrophage: postcardiotomy delirium, HIV-associated dementia and psychiatry. Prog Neurobiol 1994;42:475–88.

[14] George J, Bleasdale S, Singleton SJ. Causes and prognosis of delirium in elderly patients admitted to a district general hospital. Age Ageing 1997;26:423–7.

[15] Manos PJ, Wu R. The duration of delirium in medical and postoperative patients referred for psychiatric consultation. Ann Clin Psychiatry 1997;9:219–26.

[16] Willard LB, Hauss-Wegrzyniak B, Wenk GL. Pathological and biochemical consequences of acute and chronic neuroinflammation within the basal forebrain cholinergic system of rats. Neuroscience 1999;88:193–200.

[17] Flacker JM, Lipsitz LA. Serum anticholinergic activity changes with acute illness in elderly medical patients. J Gerontol A Biol Sci Med Sci 1999;54:M12–6.

[18] Dunlop RJ, Campbell CW. Cytokines and advanced cancer. J Pain Symptom Manage 2000;20:214–32.

[19] Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review & analysis of alternative mechanisms. Life Sci 1995;57:1011–26.

[20] Eikelenboom P, Hoogendijk WJ. Do delirium and Alzheimer's dementia share specific pathogenetic mechanisms? Dement Geriatr Cogn Disord 1999;10:319–24.

[21] Eikelenboom P, Rozemuller JM, van Muiswinkel FL. Inflammation and Alzheimer's disease: relationships between pathogenic mechanisms and clinical expression. Exp Neurol 1998;154:89–98.

[22] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[23] Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19:1015–22.

[24] Jorm AF, Scott R, Cullen JS, et al. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. Psychol Med 1991;21:785–90.

[25] Inouye SK, van Dyck SK, Alessi CH, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–8.

[26] de Rooij SE, van Munster BC, Korevaar JC, Casteelen G, Schuurmans MJ, van der Mast RC. Delirium subtype identification and the validation of the delirium rating scale-revised-98 (Dutch version) in hospitalized elderly patients. Int J Geriatr Psychiatry 2006;21:876–82.

[27] Weinberger M, Samsa GP, Schmader K, et al. Comparing proxy and patients' perceptions of patients' functional status: results from an outpatient geriatric clinic. J Am Geriatr Soc 1992;40:585–8.

[28] Wilson K, Broadhurst C, Diver M, et al. Plasma insulin growth factor-1 and incident delirium in older people. Int J Geriatr Psychiatry 2005;20:154–9.

[29] Holmes C, El-Okl M, Williams AL, et al. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003;74:788–9.

[30] Teunissen CE, van Boxtel MP, Bosma H, et al. Inflammation markers in relation to cognition in a healthy aging population. J Neuroimmunol 2003;134:142–50.

[31] Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology 2002;59:371–8.

[32] Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 2003;61:76–80.

[33] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43:183–94.

[34] Lipowski ZJ. Delirium in the elderly patient. N Engl J Med 1989;320:578–82.

[35] Trzepacz PT. Update on the neuropathogenesis of delirium. Dement Geriatr Cogn Disord 1999;10:330–4.

[36] Gibson GE, Blass JP, Huang HM, et al. The cellular basis of delirium and its relevance to age-related disorders including Alzheimer's disease. Int Psychogeriatr 1991;3:373–95.

[37] Kalman J, Juhasz A, Bogats G, et al. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. Neurochem Int 2006;48:177–80.

[38] Kobayashi K, Takeuchi O, Suzuki M, et al. A retrospective study on delirium type. Jpn J Psychiatry Neurol 1992;46:911–7.

[39] Pollmacher T, Haack M, Schuld A, et al. Low levels of circulating inflammatory cytokines—do they affect human brain functions? Brain Behav Immun 2002;16:525–32.

[40] Haack M, Hinze-Selch D, Fenzel T, et al. Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: effects of confounding factors and diagnosis. J Psychiatr Res 1999;33:407–18.