Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology

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ABSTRACT

Introduction: Delirium is a common and life-threatening neuropsychiatric syndrome. Diagnosing delirium can be challenging, which increases mortality and mortality rates and health care costs. The biologic model of delirium is not definite yet, but evidence supports a cholinergic deficiency model. Delirium may be the result of processes and drugs that trespass a compromised blood-brain barrier. We aimed to evaluate the possible diagnostic utilization and the role of certain biomarkers, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and insulin like growth factor-1 (IGF-1), in delirium etiology.

Methods: A total of 93 inpatients that planned to undergo cardiovascular surgery were informed; 35 of them completed the study. Medical history and current cognitive status were evaluated pre-operatively. Participants were followed using Delirium Rating Scale-Revised-98 Turkish (DRS-R98-T) for delirium symptoms, and blood samples were collected post-operatively.

Results: Delirium was developed more in participants who had worse pre-operative cognitive status. Also, low pre-operative IGF-1 levels were detected in the delirium group. Pre-operative CRP and TNF- α levels were not different between groups.

Conclusion: Low IGF-1 levels can be used to predict delirium after surgery. However, the complex nature of cytokines and delirium itself make it difficult to utilize cytokines to predict delirium instead of psychometric tools. (Archives of Neuropsychiatry 2014; 51: 376-382)

Key words: Delirium, CRP, TNF- α , IGF-1, DRS-R98-T

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Introduction

Delirium is an acute neuropsychiatric syndrome, characterized by impairments in higher cortical functions (such as cognition, behavior, thought, and language) arising from physiological or structural dysfunctions caused by internal, surgical, or pharmacological abnormalities (1). The core features of delirium are symptoms with a sudden onset, which then fluctuate throughout the day and are generally reversible (2).

The incidence of delirium has been reported at different rates depending on the clinic in which the study was conducted. In hospitalized geriatric patients, delirium has been reported at rates between 9%–43% (3,4), and this can rise up to 47% follow-

ing surgery (5). After heart surgery, delirium has been reported to develop at rates of 12%–27% (6), although these rates only show the frequency of clinically diagnosed patients. Depending on the physician's field of specialization, the diagnosis has been reported to be overlooked in up to two thirds of delirium cases (7). This results in increased morbidity and mortality rates and increased healthcare costs with prolonged hospitalization (8,9). Furthermore, hospital mortality rates have been reported to increase approximately 22-fold in patients diagnosed with delirium (10).

The presence of a variety of factors in the etiology constitutes an obstacle to the development of reliable diagnostic tools for delirium, which is a clinical syndrome. Although a wide

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range of etiological factors with different physiological effects constitute delirium, the signs of delirium have stereotypical characteristics referred to as the "Core symptoms." This indicates that delirium has evolved as a result of the effects on certain neural pathways. Hence, it is considered that mediators, some neurotransmitters, and cytokines, which affect these neural pathways, are directly involved in the etiology of delirium (11). C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), and insulin-like growth factor-1 (IGF-1) are cytokines that have been reported to be involved in the pathophysiology of delirium in the literature. IGF-1 is neuroprotective and inhibits cytotoxic cytokines, whereas TNF- α is a cytotoxic cytokine. The possible role of CRP in the pathophysiology of delirium is reflected in the manner that other factors (e.g., cytokines or IGF-1) are involved in the process (12,13).

Vascular endothelial cells and perivascular cells, located between the peripheral blood and brain parenchymal cells, play a role in the transport of inflammation from the periphery to the brain. It has been reported that activated parenchymal microglial cells reach the brain in response to systemic inflammation, despite an intact blood-brain barrier, and the cytokine expression associated with this disrupts neural transmission without causing structural damage in the brain.

Cytokines may affect the activity of catecholamines, indolamines, gamma-amino butyric acid (GABA), and acetylcholine (14,15). This mechanism has been suggested to lead to the development of delirium (16). Therefore, revealing the biological markers that facilitate the diagnosis of the disease will improve the specificity of the diagnosis and will affect morbidity, mortality, and costs in a positive way by creating the opportunity for early diagnosis. In this study, it was aimed to determine the role of CRP, TNF- α , and IGF-1 in the etiology of delirium and the possibilities of diagnostic use of these markers.

Methods

Cases

Because there is a relatively high incidence of delirium after cardiac surgery (6), the study initially enrolled 95 patients for whom coronary artery bypass surgery was planned at the Gulhane Military Medical Faculty (GMMF), Department of Cardiovascular Surgery between January 2010 and July 2011. Informed consent was obtained from all the patients. Three patients did not undergo the planned surgery, and 57 patients were excluded for various other reasons [verbal request to withdraw from the trial ($n=32$), blood samples determined as unsuitable for analysis ($n=13$), and deficiency of collected blood samples ($n=12$)]. Therefore, the study was completed with 35 patients. The development of postoperative delirium was followed prospectively. After the surgery, the study group comprised 15 patients who developed delirium, and the control group was formed of 20 patients who did not develop delirium.

Approval for the study was granted by the 7th Ethics Committee/Ankara on 01.13.2010 with No.18 and supported by the Scientific Council of Gulhane Military Medical Academy.

Data Collection Tools

The data for this study was obtained in face-to-face interviews using a specifically developed data collection form. Age, gender, education, health status, and drug information data was provided by the patients themselves and/or from caregivers and was confirmed by the medical records. The presence of any psychiatric disorder was assessed by the investigator with the help of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) form, and the premorbid cognitive status of the patients was evaluated using the mini-mental status examination (MMSE) and the clock drawing test (CDT).

Mini-Mental Status Examination (MMSE)

MMSE is a screening test, consisting of 11 items under five main headings of orientation, record memory, attention, mathematical calculation, and recall (17). The scale has been reported to be valid and reliable in the diagnosis of mild dementia after standardization for the Turkish population with 5 years of primary education (18). The maximum MMSE score is 30 points; a score of 24–30 suggests normal status, 20–23 suggests mild dementia, 10–19 suggests moderate dementia, and 0–9 indicates severe dementia (17,18).

Clock Drawing Test (CDT)

In CDT, the participants were asked to draw a clock image and place the numbers in the correct position on the image. There is no time limitation for the test. CDT scoring has been described in detail in the literature (19).

Delirium Rating Scale, Revised-98-T (DRS-R98-T)

The DRS-R98-T was produced in 1998 from a revised version of the Delirium Rating Scale developed in 1989 by Trzepacz. A validity-reliability study of the DRS-R98-T scale was conducted in the GMMF Department of Psychiatry (20).

Delirium Diagnosis and Follow-Up

Patients were screened daily with the DRS-R98-T for symptoms of delirium from postoperative Day 2 to Day 7. In the event of the appearance of symptoms, delirium was diagnosed using the diagnostic criteria mentioned in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR), and those patients were included in the study group. Following a diagnosis of delirium, patients were assessed with DRS-R98-T in the morning and in the evening at 12-h intervals.

Laboratory Evaluation

Venous blood samples of patients were drawn on the day before the scheduled surgery and on postoperative Day 2 between 06:00 and 08:00. Whole blood count and serum SGOT,

SGPT, urea, creatinine, and albumin measurements were performed on the same day. Following collection of all the samples, CRP, TNF- α , and IGF-1 measurements were performed on the same day in one session using the serum samples that had been centrifuged for 10 min at 4000 rpm and stored at -80°C. These cytokines were measured using commercial enzyme-linked immunosorbent assay kits.

Statistical Analysis

Data were described using percentage, mean $\pm$ standard deviation, and median (min-max). The Mann-Whitney U-test was used for between-group comparisons, and the Wilcoxon test was used for within the group comparisons. A value of $p < .05$ was considered statistically significant. Compilation and statistical evaluation of the data were made using the Statistical Package for the Social Sciences (SPSS for Windows, version 16.0. Chicago, IL, USA SPSS, Ltd. 2007).

Results

Characteristics of Patients and Medical History

The study comprised a total of 35 patients; 15 (7 male, 8 female) who developed delirium after surgery and 20 (1 female, 19 male) who did not develop delirium. The characteristics of the patients are given in Table 1. The groups were similar in terms of age and educational status ($p = .085$ and $p = .47$, respectively). The only statistically significant difference observed between the two groups was in the history of cataract surgery, which has been reported to be a risk factor in the development of delirium. The incidence of cataract surgery was significantly higher in the group of patients who developed delirium ($p < .05$). Although all patients were taking some form of continuous medication for various diseases, none of these drugs may result in delirium.

Neuropsychological Findings

The mean MMSE score of patients who developed delirium was lower than the score of the control group (26.25 ± 2.87 and 28.3 ± 2.1 , respectively, $Z = -3.14$, $p = .002$). Similarly, there was a significant difference between the results of CDT (study group, 2.86 ± 1.18 ; control group, 3.05 ± 0.94 ; $Z = -2.04$, $p = .041$).

Laboratory Findings

The groups were compared in terms of white blood cell count, serum SGOT, SGPT, urea, creatinine, and albumin levels to exclude causes such as infection, liver and kidney failure, and hypoalbuminemia that may predispose to the development of delirium. There was no significant difference between the groups in these parameters.

An increase in CRP was observed in all patients after surgery. This increase was significant in both groups according to the preoperative values (control group, $Z = -2.054$, $p = .04$; patients who developed delirium, $Z = 2.713$, $p = .007$) (Table 2). The

Table 1. Socio-demographic characteristics

	All patients (n=35)	Delirium patients (n=15)	Controls (n=20)
Age*	64.2 $\pm$ 10.3	69.0 $\pm$ 9.6	60.7 $\pm$ 11.9
Gender	8 K, 27 E	7 K, 8 E	1 K, 19 E
Educational Status			
No Education	10	5	5
Elementary School	11	5	6
Middle School	5	3	2
High School	7	1	6
Tertiary Education	2	1	1
Medical History			
Carotid artery stenosis	6	2	4
Psychiatric disorders (dementia)	5 (2)	3 (1)	2 (1)
Trauma (head injury)	6 (3)	3 (2)	3 (1)
Cataract op.†	9	7	2
Accompanying Diseases	28	13	15
Hypertension	12	6	6
Type 2 DM	7	3	4
Type 2 DM + Hypertension	2	1	1
Other medical conditions	7	3	4
*(mean $\pm$ SD)			
†($\chi^2 = 5.316$, $p = .024$ chi-square test)			

difference was significant in the comparison of the difference between the groups in CRP levels that were associated with the procedure. The difference observed in patients who developed delirium was higher ($Z = -.695$, $p = .02$). Although TNF- α and IGF-1 levels increased postoperatively, these increases were not statistically significant. The cytokine levels assessed in this study are presented in Table 2. The preoperative IGF-1 levels of the group of patients who developed delirium was found to be lower than that of the control group ($Z = -.700$, $p = .048$) (Figure 1).

Discussion

The incidence of delirium in the current study population was observed to be 16.3% (15/92). In a clinic where a study of the incidence of delirium was conducted, sociodemographic characteristics and individual differences such as comorbidities were reported to have an effect (13). In other studies, delirium has been reported to develop at 12-27% after cardiovascular surgery (14). The rate determined in the current study is consistent with literature. The relatively older age of patients who are to undergo cardiovascular surgery associated with atherosclerotic heart disease is known to have an effect on the incidence of delirium (15). In a study by Tsutsui et al. (16) in 1996,

Table 2. Cytokine levels in patients with delirium and controls

	Controls (n=20)			Delirium group (n=15)					
	Pre-op	Post-op	p	Pre-op	Post-op	p	Attack	p [*]	p [†]
CRP-hs (mg/mL)	.048±.013	.054±.013	.04	.041±.019	.054±.011	0.007	.055±.017	.25	.227
TNF-α (pg/mL)	21.2±21.4	28.2±48.5	.27	23.8±26.3	28.2±28.3	0.74	20.7±14.9	.39	.956
IGF-1 (ng/mL)	1439±1755	2133±2941	.48	1029±1183	1405±1809	0.07	1023±1049	.67	.048

*p (pre-op - attack)

†p (control group pre-op - pre-operative patients with delirium)

Figure 1. IGF-1 values in controls and patients with delirium.

it was reported that following emergency surgery, patients aged over 80 years developed delirium at the rate of 50% and in patients aged below 50 years, after emergency or elective surgery, no delirium developed. In the current study, the median age of the control group was 62 years and of the group which developed delirium, 72 years. Although the age difference between the two groups was not determined to be statistically significant it is still noticeable that the age of the patient group that developed delirium was older. This is consistent with the data that delirium develops more in patients of an advanced age. Despite a low level of differentiation power on this subject because of cognitive failure, an evaluation made using the Mini-Mental Test (MMT) is known to have provided important information on the subject of the current cognitive status. Patients with a low MMT performance preoperatively have been reported to develop delirium at a higher rate (17). Some studies have claimed that the Clock Drawing Test (CDT) is more valuable than the MMT in the prediction of delirium (18). However, there are studies which report that neither the MMT nor the CDT are a suitable means of predicting the development of delirium in patients undergoing heart surgery (19). In the current study, a statistically significant difference was observed between the control group and the patient group that developed delirium in terms of the points scored in the MMT and CDT applied preoperatively to determine the

existing cognitive status. When the MMT points of the groups were compared, the points of the control group were 28.3 ± 2.1 , and of the delirium group, 25.6 ± 2.87 and it could be understood that the difference between the groups was statistically significant ($p=.002$). A statistically significant difference was also determined between the groups in the CDT points ($p=.041$). The results of this study suggest that the cognitive status revealed by the screening tests could be a significant indicator in the prediction of the development of delirium in patients who do not have dementia (20).

Ageing, caused by increased natural immunity activity, is a low level inflammatory condition (20,21,22). Inflammation is related to several morbid conditions in the elderly such as cardiovascular status (23), addictions (24) and Alzheimer's disease (25). Inflammation has been shown to lead to the breakdown of the blood-brain barrier (26) and decrease cholinergic transfer (27). The majority of studies which have examined the relationship between cytokine levels and delirium have been small and cross-sectional. In other studies conducted on medical and surgical populations, there has been reported to be a higher rate of one or more indications of inflammation in patients with delirium compared to other patients (28,29). In a study by De Rooij (30), elevated levels of IL-6, IL-8 and CRP were determined in elderly hospitalised patients with delirium. A relationship has been reported between confusion and elevated CRP and IL-6 levels in elderly patients postoperatively (31,32,33). CRP is the most commonly used marker of inflammation.

Two small-scale studies conducted on elderly patients who presented at internal medicine clinics with acute complaints reported that a high level of CRP and a low level of IGF-1 were risk factors for the development of delirium (34,35). In another study which researched the relationship of CRP and IGF levels before hip fracture surgery with the development of delirium, no relationship was determined between CRP values and the development of delirium (36). In the current study, no statistically significant difference was determined between the control group patients and those who developed delirium in respect of preoperative CRP levels ($p=.23$). Postoperatively the CRP values in both the control and the delirium group were found to be statistically significantly higher than the preoperative values (con-

trol group, $p=.04$; delirium group, $p=.007$). A more evident post-operative change in the CRP values was observed in the patient group that developed delirium than in the control group ($p=.02$). That no difference was found between the groups in respect of the preoperative CRP values is consistent with the results reported by Lemistra.

That different CRP values were not determined in the patients who developed delirium compared to the control group makes it difficult to consider CRP value as an independent risk factor in the development of delirium. However, that the change in CRP was statistically significantly different in the patient group that developed delirium compared to the control group is consistent with results reported for IL-6 and TNF. This suggests that inflammation response has a role in the pathophysiology of delirium. In another study researching the cytokine and chemokine levels of a control group and a group which developed delirium in patients undergoing cardiovascular surgery the TNF- α values were examined preoperatively and at postoperative 6 hours and 4 days. No statistically significant difference was determined in the preoperative or postoperative TNF- α values (37). Similar results were also reported in another study (38).

In the current study, no statistically significant change was determined in the preoperative and postoperative TNF- α values (control group, $p=.27$; delirium group, $p=.74$). This finding was similar to the results of the previously mentioned studies (38,39). That there was no difference observed in the CRP and TNF- α values can be explained by there being no infection because the study population was formed of patients being prepared for elective surgery. Just as with CRP, that there was no difference shown between the groups in the preoperative and postoperative TNF- α value, which is a pro-inflammatory cytokine, made it difficult to consider to consider TNF- α as an independent risk factor for the development of delirium. According to the results of a study conducted on 100 consecutive patients hospitalised in the emergency internal medicine clinic, low levels of IGF-1 could be useful in halting the development of delirium (38). In another study, an elevated level of IL-6 and a decreased level of IGF-1 were found in cases of acute internal disease with delirium (39,40).

In two other small-scale studies conducted on elderly patients presenting at internal medicine clinics, it was reported that high CRP and low IGF-1 levels were risk factors for the development of delirium (34,35). In a meta-analysis by Awert et al. (41) of the effect of the IGF-1 value on the cognition of healthy elderly individuals, a positive correlation was determined between MMT points and the IGF-1 value. There are studies which have suggested that somatostatin and IGF-1 improved cognitive functions in patients with cognitive insufficiency and could be used in the prevention and treatment of delirium (42). In the current study, the pre-operative IGF-1 levels were found to be lower in the patients who developed delirium compared to the control group ($p=.048$). In contrast, the change occurring in the IGF-1 values during surgery were not statistically significant (control

group, $p=.48$; delirium group, $p=.07$). IGF-1 should be classified separately from other cytokines as the neuroprotective effect of IGF-1 plays an important role in accelerating the development of MSS, neuron life, proliferation, differentiation and synaptogenesis. It is thought that a decrease in the protective effect of IGF-1 on neurons could be a risk factor in the development of delirium (41).

In the interpretation of the cytokine results obtained, some points must be taken into consideration. When inflammation markers form a response to stress, they have a tendency to rise and fall together as a mass. Therefore, inflammation markers must be interpreted together. In addition, inflammation markers are affected by other risk factors of delirium such as age, type of stressor and comorbidities, so these factors must be taken into consideration in the evaluation (37). As delirium is a clinical syndrome there is no gold standard pathology method for diagnosis.

The fluctuating nature of the delirium table makes it difficult to predict the times for the application of diagnostic tests. A similar difficulty of delirium is that it is a central nervous system process, so serum markers are used during monitoring. In addition, as patient groups of those who develop delirium comprise patients of advanced age hospitalised for relatively acute illnesses, there is an effect on the process of the type of acute disease, the characteristics, other concomitant pathologies and medications used (38). Apart from the above-mentioned general restrictions, the high number of patients excluded from the current study reduced the strength of the study findings. The aim of this study was to determine possible biological markers for use in the delirium table.

According to the findings of the study, no statistically significant difference was determined between the control group and the study group of patients who developed delirium in respect of CRP and TNF- α values. The CRP values measured postoperatively showed a greater change from the pre-operative values in the delirium group than in the control group and the pre-operative IGF-1 level was found to be lower in the delirium group than in the control group. In the retrospective examination, the cognitive status screening tools used were observed to be useful in the prediction of the development of delirium.

In the light of these findings, the measurement of pre-operative IGF-1 levels and inclusion in the models used to predict delirium which may develop post-operatively, may be useful in predicting the delirium table. Evaluation of each patient who is to undergo surgery with pre-operative cognitive status screening tests may be appropriate for use in the prediction of the potential delirium table which may develop postoperatively, but it can be considered that the use of clinical tools together with biological markers would give more useful results.

References

1. Trzepacz PT, Bourne R, Zhang S. Designing clinical trials for the treatment of delirium. *J Psychosom Res* 2008; 65:299-307. [CrossRef]

2. Trzepacz PT, Meagher DJ. Neuropsychiatric aspects of delirium. In Yudofsky SC, Hales RE, editörler. American Psychiatric Publishing Textbook of Neuropsychiatry and Clinical Neurosciences içinde. 5. Baskı. Washington DC: American Psychiatric Publishing; 2007 s. 445-517.
3. Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Confusion assessment method in the diagnostics of delirium among aged hospital patients: would it serve better in screening than as a diagnostic instrument? *Int J Geriatr Psychiatry*. 2002; 17:1112-1119. [\[CrossRef\]](#)
4. O'Keeffe ST, Gosney MA. Assessing attentiveness in older hospital patients: global assessment versus tests of attention. *J Am Geriatr Soc*, 1997; 45:470-473.
5. Agbayewa MO. Recognition of organic mental disorders by physicians. *CMAJ* 1983; 15; 128:927-928.
6. Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Geriatr Psychiatry* 1992; 40:601-6.
7. Johnson JC, Kerse NM, Gottlieb GL, Wanich C, Sullivan E, Chen K, Prospective versus retrospective methods of identifying patients with delirium. *J Geriatr Psychiatry* 1992; 40:316-319.
8. Hustey FM, Meldon SW, Smith MD, Lex CK. The effect of mental status screening on the care of elderly emergency department patients. *Ann Emerg Med* 2003; 41:678-684. [\[CrossRef\]](#)
9. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J. Phenomenology of delirium. Assessment of 100 adult cases using standardized measures. *Br J Psychiatry* 2007; 190:135-141. [\[CrossRef\]](#)
10. 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; 12:189-198. [\[CrossRef\]](#)
11. Güngen C, Ertan T, Eker E, Yaşar R. Standardize mini mental test'in Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. *Türk Psikiyatri Derg* 2002; 13:273-281
12. Cangöz B, Karakoç E, Selekler K. The norm determination and validity-reliability studies of clock drawing test on Turkish adults and elderly (ages 50 and over). *Turk J Geriatr* 2006; 9:136-142.
13. Burns A, Gallagley A, Byrne J, Delirium. *J Neurol Neurosurg Psychiatr* 2004; 75:362-367. [\[CrossRef\]](#)
14. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, Jaszewski R, Sobow T, Kloszewska I. Clinical utility and use of DSM-IV and ICD-10 Criteria and The Memorial Delirium Assessment Scale in establishing a diagnosis of delirium after cardiac surgery. *Int J Psychosom* 2008; 49:73-76. [\[CrossRef\]](#)
15. Bucerius J, Gummert JF, Borger MA. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg* 2004; 127:57-64. [\[CrossRef\]](#)
16. Tsutsui S, Kitamura M, Higashi H, Matsuura H. Development of postoperative delirium in relation to a room change in the general surgical unit. *Surg Today* 1996; 26:292-294. [\[CrossRef\]](#)
17. Hideyuki H Hattori, Junichi J Kamiya, Hiroshi H Shimada, Hirotohi H Akiyama, Akihiro A Yasui, Kojiro K Kuroiwa, Koji K Oda, Masahiko M Ando, Takashi T Kawamura, Atsushi A Harada, Yuichi Y Kitagawa, Shinji S Fukata. Assessment of the risk of postoperative delirium in elderly patients using E-PASS and the NEECHAM Confusion Scale. *Int J Geriatr Psychiatry* 2009; 24:1304-1310. [\[CrossRef\]](#)
18. Manos PJ. The utility of the ten-point clock test as a screen for cognitive impairment in general hospital patients. *Gen Hosp Psychiatry* 1997; 19:439-444. [\[CrossRef\]](#)
19. Rolfson DB, McElhaney JE, Jhangri GS, Rockwood K. Validity of the Confusion Assessment Method in Detecting Postoperative Delirium in the Elderly. *Int Psychogeriatr* 1999; 11:431-438. [\[CrossRef\]](#)
20. Godbout JP, Johnson RW. Age and neuroinflammation: a lifetime of psychoneuroimmune consequences. *Immunol Allergy Clin North Am* 2009; 29:321-337. [\[CrossRef\]](#)
21. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Curr Transl Geriatr Exp Gerontol Rep* 2004; 39:687-99.
22. Federico F Licastro, Giuseppina G Candore, Domenico D Lio, Elisa E Porcellini, Giuseppina G Colonna-Romano, Claudio C Franceschi, Calogero C Caruso. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. *Immun Ageing* 2005; 2:8. [\[CrossRef\]](#)
23. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004 351:2599-2610. [\[CrossRef\]](#)
24. Ferrucci L, Cavazzini C, Corsi AM, Bartali B, Russo CR, Lauretani F, Bandinelli S, Bandinelli S, Guralnik JM. Biomarkers of frailty in older persons. *J Endocrinol Invest* 2002; 25:10-15.
25. Birkenhäger WH, Staessen JA. Convergence of atherosclerosis and Alzheimer's disease. *Lancet* 2004; 19:363:2092.
26. Jeppsson B, Freund HR, Gimmon Z, James JH, Meyenfeldt von MF, Fischer JE. Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? *Am. J. Surg* 1981; 141:136-142. [\[CrossRef\]](#)
27. Hammond EJ, Meador KJ, Aung-Din R, Wilder BJ. Cholinergic modulation of human P3 event-related potentials. *Neurology* 1987; 37:346-350. [\[CrossRef\]](#)
28. Kudoh A, Takase H, Takahira Y, Katagai H. Postoperative confusion in schizophrenic patients is affected by interleukin-6. *J Clin Anesth* 2003; 15:455-462. [\[CrossRef\]](#)
29. Visvanathan K, Sundararajan V, Pugach P, Zabriskie JB. Postoperative cognitive decline: association with preoperative tumor necrosis factor-alpha levels. *J Am Geriatr Soc* 2003; 51:1673-1674. [\[CrossRef\]](#)
30. Buurman BM, Hoogerduijn JG, de Haan RJ, Abu-Hanna A, Lagaay AM, Verhaar HJ, Schuurmans MJ, Levi M, de Rooij SE. Geriatric Conditions in Acutely Hospitalized Older Patients: Prevalence and One-Year Survival and Functional Decline. *PLoS ONE* 2011; 14:6:e26951.
31. Beloosesky Y, Grinblat J, Pirotsky A, Weiss A. Different C-reactive protein kinetics in post-operative hip-fractured geriatric patients with and without complications. *Gerontology* 2004; 50:216-222. [\[CrossRef\]](#)
32. Yichayaou Y Beloosesky, David D Hendel, Avraham A Weiss, Avital A Hershkovitz, Joseph J Grinblat, Anatoly A Pirotsky, Vivian V Barak. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. *J Gerontol A Biol Sci Med Sci* 2007; 62:420-426. [\[CrossRef\]](#)
33. Kudoh A, Takase H, Katagai H, Takazawa T. Postoperative interleukin-6 and cortisol concentrations in elderly patients with postoperative confusion. *Neuroimmunomodulation* 2005; 12:60-6. [\[CrossRef\]](#)
34. Macdonald A, Adamis D, Treloar A, Martin F. C-reactive protein levels predict the incidence of delirium and recovery from it. *Age Ageing* 2007; 36:222-225. [\[CrossRef\]](#)
35. Wilson K, Broadhurst C, Diver M, Jackson M, Mottram P. Plasma insulin growth factor-1 and incident delirium in older people. *Int J Geriatr Psychiatry*. 2005; 20:154-159. [\[CrossRef\]](#)
36. Lemstra AW, Kalisvaart KJ, Vreeswijk R, van Gool WA, Eikelenboom P. Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients. *Int J Geriatr Psychiatry* 2008; 23:943-948. [\[CrossRef\]](#)

37. Rudolph JL, Ramlawi B, Kuchel GA, McElhaney JE, Xie D, Sellke FW, Khabbaz K, Levkoff SE, Marcantonio ER. Chemokines are associated with delirium after cardiac surgery. *J Gerontol A Biol Sci Med Sci* 2008; 63:184-189. [\[CrossRef\]](#)
38. Adamis D, Lunn M, Martin FC, Treloar A, Gregson N, Hamilton G, Macdonald AJ. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009; 38:326-32; discussion 251. [\[CrossRef\]](#)
39. van Steijn JH, Nieboer P, Hospers GA, de Vries EG, Mulder NH. Delirium after interleukin-2 and alpha-interferon therapy for renal cell carcinoma. *Anticancer Res* 2001; 21:3699-3700.
40. Malek-Ahmadi P, Hilsabeck RC. Neuropsychiatric complications of interferons: classification, neurochemical bases, and management. *Ann Clin Psychiatry* 2007; 19:113-123. [\[CrossRef\]](#)
41. Arwert LI, Deijen JB, Drent ML. The relation between insulin-like growth factor I levels and cognition in healthy elderly: a meta-analysis. *Growth Horm. IGF Res* 2005; 15:416-422. [\[CrossRef\]](#)
42. Craft S, Asthana S, Newcomer JW. Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999; 56:1135-1140. [\[CrossRef\]](#)