Neuroinfiammazione, neurodegenerazione, delirium

Giuseppe Bellelli
La fisiopatologia del delirium: sette ipotesi

Maldonado J. Am J Geriatr Psych 2013
Vi è relazione tra delirium e infiammazione?
C-reactive protein levels predict the incidence of delirium and recovery from it

**Key points**

- High levels of CRP independently predicted incidence of delirium
- A higher initial MMSE and low CRP predicted the recovery from delirium at any time during hospitalization
- CRP in acute illness merits further investigation as a marker for potential precipitating or perpetuating mechanisms for delirium

*MacDonald et al, Age Ageing 2007*
Chemokines Are Associated With Delirium After Cardiac Surgery


Methods. Serum samples were drawn from 42 patients undergoing cardiac surgery preoperatively and postoperatively at 6 hours and postoperative day 4. The serum concentrations of 28 inflammatory markers were determined with a microsphere flow cytometer. A priori, inflammatory markers were assigned to five classes of cytokines. A class \( z \) score was calculated by averaging the standardized, normalized levels of the markers in each class. Beginning on postoperative day 2, patients underwent a daily delirium assessment.

Results. Twelve patients with delirium were matched by surgical duration, age, and baseline cognition to 12 patients without delirium. At the 6-hour time point, patients who went on to develop delirium had higher increases of chemokines compared to matched controls (class \( z \) score 0.3 ± 1.0, \( p < .05 \)). Among the five classes of cytokines, there were no other significant differences between patients with or without delirium at either the 6 hour or postoperative day 4 assessments.

Conclusion. After cardiac surgery, chemokine levels were elevated in patients who developed delirium in the early postoperative period. Because chemokines are capable of disrupting blood–brain barrier integrity in vitro, future studies are needed to define the relationship of these inflammatory mediators to delirium pathogenesis.

Comparison of levels of (A) interleukin (IL)-6 and (B) interleukin-8 in patients with and without delirium

Van Munster B et al, JAGS 2008
Autoregulation, C-reactive protein, S-100β, and cortisol in patients with and without sepsis-associated delirium

Pfister et al, Crit Care 2008
High Preoperative Plasma Neopterin Predicts Delirium After Cardiac Surgery in Older Adults

Robert J. Osse, MD,* Durk Fekkes, PhD,* Joke H. M. Tulen, PhD,* André I. Wierdsma, PhD,* Ad J. J. C. Bogers, MD, PhD,† Rose C. van der Mast, MD, PhD,‡ and Michiel W. Hengeveld, MD, PhD*
Cerebrospinal fluid (CSF) interleukin (IL)-8 levels (pg/mL) in patients with (n=515) and without (n=521) perioperative delirium

$p=.003^*$
Long-term sequelae of severe sepsis: cognitive impairment and structural brain alterations – an MRI study (LossCog MRI)

Theresa Götz\textsuperscript{1,3∗†}, Albrecht Günther\textsuperscript{2,3†}, Otto W Witte\textsuperscript{2,3}, Frank M Brunkhorst\textsuperscript{3,4}, Gundula Seidel\textsuperscript{3,5} and Farsin Hamzel\textsuperscript{3,5}

Methods/Design: This is a prospective, controlled observational study. We are in the process of recruiting 25 survivors of severe sepsis or septic shock who will be investigated with functional MRI (fMRI), T1-weighted MRI, and Diffusion Tensor Imaging (DTI) as well as Magnetoencephalography (MEG). Furthermore, patients will undergo neuropsychological evaluation using the DemTect and the clock drawing tests. In addition, verbal and declarative memory is assessed by the Verbal Learning and Memory Test. The primary aim is to determine the volumetry of the amygdala and the hippocampus. The secondary aim is to analyze the relationship between cognitive tests and MEG, and the (f)MRI results. Moreover, a between-group comparison will be evaluated to an age-matched group of healthy controls.

Discussion: In a previous MEG study, we observed a significant slowing of the prominent background activity in sepsis survivors and hepatic encephalopathy patients in particular shortly after discharge from the ICU. Intriguingly, the rhythmic brain activity after visual flickering stimulation was altered in sepsis survivors in comparison to age-matched healthy volunteers. Various interconnected brain regions. The current project will analyze whether the modifications are related to a damage of the fibers connecting different brain regions or to a disturbance of the functional interaction between different brain regions or even due to an atrophy of certain brain regions.

Götz et al. BMC Neurology 2014, 14:145
http://www.biomedcentral.com/1471-2377/14/145
I possibili link fisiopatogenetici
Inflammation: routes of communication from the periphery to CNS
<table>
<thead>
<tr>
<th>System</th>
<th>Sample mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory system</strong></td>
<td>TNF-α</td>
</tr>
<tr>
<td></td>
<td>IL-1β</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
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<td>IL-8</td>
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<td></td>
<td>PGE2</td>
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<tr>
<td></td>
<td>IFNα/IFN β</td>
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<tr>
<td><strong>Sympathetic nervous system</strong></td>
<td>Acetylcholine</td>
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<tr>
<td></td>
<td>Noradrenaline</td>
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<tr>
<td></td>
<td>Adrenaline</td>
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<tr>
<td><strong>LHPA axis</strong></td>
<td>Corticotropin-releasing hormone</td>
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<td></td>
<td>ACTH</td>
</tr>
<tr>
<td></td>
<td>Cortisol</td>
</tr>
<tr>
<td></td>
<td>Vasopressine</td>
</tr>
</tbody>
</table>

MacLullich A, J Psychosom Res 2008
Cytokine-induced sickness behaviour: mechanisms and implications

Jan Pieter Konsman, Patricia Parnet and Robert Dantzer

TRENDS in Neurosciences Vol.25 No.3 March 2002

Invited minireview

The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease


Twenty years of research on cytokine-induced sickness behavior

Robert Dantzer a,b,* , Keith W. Kelley a

The degree of brain endothelial and perivascular cell activation in human post-mortem brains is correlated with the degree of systemic inflammation (Uchikado H, 2004).

Blood brain barrier exhibits structural and functional changes with ageing (Mooradian A, 1994), diabetes (Starr M, 2003), AD (Bowman G, 2007) and vascular dementia (Skoog I, 1998), and this may inappropriately increase the strength of inflammatory signaling.
The cytokine-induced sickness behavior

Range of Behavioral Effects Observed in Laboratory Rodents Injected Systemically or Centrally with Proinflammatory Cytokines and the Cytokine Inducer Lipopolysaccharide

Behavioral effects

- Decreased general activity
- Decreased exploratory behavior
- Decreased social and sexual behavior
- Decreased food and water intake
- Decreased preference for saccharin
- Decreased brain self-stimulation
- Decreased body care activities
- Impaired learning and memory

Dantzer R, Brain Behav Imm 2001; 15:7:24
Data are expressed as a percentage of β-2 microglobulin mRNA expression used as an internal control.
Fast immune-to-brain signaling mediated by vagal nerve conduction

Dantzer R, Brain Behav Imm 2001; 15:7:24
The cytokine-induced sickness behavior

Dantzer R, Brain Behav Imm 2001; 15:7:24
Aberrant stress responses

(a) an abnormally intense stress or inflammatory response, with increased and/or inappropriately sustained levels of signalling molecules such as cortisol or
(b) an exaggerated response of the target tissue to normal levels of stress or inflammatory signals.

These acute stress responses are mediated by humoral and neural signalling pathways, and the interactions of these signals with CNS pathology make this category mechanistically distinct from the ‘direct brain insults’
Infiammazione ed attivazione neuroendocrina

Dinkel H et al, J Neurovirol 2002; 8:513e528
Schematic illustration of neural immune connections

Maldonado J. Am J Geriatr Psych 2013
Microglia activation in sepsis: a case-control study
Afina W Lemstra*1, Jacqueline CM Groen in’t Woud1, Jeroen JM Hoozemans2, Elise S van Haastert2, Annemiek JM Rozemuller2, Piet Eikelenboom1 and Willem A van Gool1

A

CD68 cortex  

score

p = 0.002

sepsis control

B

CD68 white matter  

score

p = 0.011

proportion of patients

0% 10% 20% 30% 40% 50% 60% 70% 80%

1 2 3
E in un cervello già danneggiato?
Systemic inflammation, delirium and cognitive decline

Cunningham C. Biochem. Soc. Trans. 2011
Systemic Inflammation Induces Acute Behavioral and Cognitive Changes and Accelerates Neurodegenerative Disease

Colm Cunningham, Suzanne Campion, Katie Lunnon, Carol L. Murray, Jack F.C. Woods, Robert M.J. Deacon, J. Nicholas P. Rawlins, and V. Hugh Perry
Systemic Inflammation Induces Acute Behavioral and Cognitive Changes and Accelerates Neurodegenerative Disease

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Effect on the progression of prion disease
Systemic inflammatory events may trigger delirium and contribute to pathological burden.

Cunningham C. Biochem. Soc. Trans. 2011
Systemic inflammatory events may trigger delirium and contribute to pathological burden.

Cunningham C. Biochem. Soc. Trans. 2011
C-reactive protein (CRP) and cytokine kinetics curves in hip-fracture-operated IMS patients, compared to cognitively normal patients

Ma è delirium o demenza?
Interleukin-18 produced by peripheral blood cells is increased in Alzheimer’s disease and correlates with cognitive impairment

Paola Bossù a,*, Antonio Ciaramella a, Francesca Salani a, Federica Bizzoni a, Erika Varsi a, Fulvia Di Iulio a, Franco Giubilei b, Walter Gianni c, Alberto Trequattrini d, Maria Luisa Moro a, Sergio Bernardini e, Carlo Caltagirone a,f, Gianfranco Spalletta a,g
Inflammatory markers and the risk of Alzheimer disease
The Framingham Study

Z.S. Tan, MD, MPH
A.S. Beiser, PhD
R.S. Vasan, MD
R. Roubenoff, MD, MHS
C.A. Dinarello, MD
T.B. Harris, MD, MS
E.J. Benjamin, MD, ScM
R. Au, PhD
D.P. Kiel, MD, MPH
P.A. Wolf, MD
S. Seshadri, MD

**ABSTRACT**

**Objective:** To examine whether serum cytokines and spontaneous production of peripheral blood mononuclear cell (PBMC) cytokines are associated with the risk of incident Alzheimer disease (AD). **Methods:** We followed 691 cognitively intact community-dwelling participants (mean age 79 years, 62% women) and related PBMC cytokine production (tertiles of spontaneous production of interleukin 1 [IL-1], IL-1 receptor antagonist, and tumor necrosis factor α [TNF-α]) and serum C-reactive protein and interleukin 6 (IL-6) to the risk of incident AD. **Results:** Adjusting for clinical covariates, individuals in the top two tertiles (T2 and T3) of PBMC production of IL-1 or the top tertile (T3) of PBMC production of TNF-α were at increased risk of developing AD (multivariable-adjusted hazard ratio [HR] for IL-1 T2 = 2.84, 95% CI 1.09 to 7.43; p = 0.03 and T3 = 2.61, 95% CI 0.96 to 7.07; p = 0.06; for TNF-α, adjusted HR for T2 = 1.30, 95% CI 0.53 to 3.17; p = 0.57 and T3 = 2.59, 95% CI 1.09 to 6.12; p = 0.031) compared with those in the lowest tertile (T1). **Interpretation:** Higher spontaneous production of interleukin 1 or tumor necrosis factor α by peripheral blood mononuclear cells may be a marker of future risk of Alzheimer disease (AD) in older individuals. These data strengthen the evidence for a pathophysiologic role of inflammation in the development of clinical AD.

**NEUROLOGY** 2007;68:1902-1908
Delirium: criteri del DSM-5

A. Disturbo dell’attenzione (i.e., ridotta capacità a dirigere, focalizzare, sostenere e shiftare l’attenzione) e consapevolezza (ridotto orientamento se nell’ambiente).

B. Il deficit si sviluppa in un periodo di tempo relativamente breve (generalmente ore o pochi giorni), rappresenta un cambiamento dai livelli di attenzione e consapevolezza di base, e tende a fluttuare in gravità nel corso della giornata.

C. É presente un altro deficit cognitivo (es, memoria, disorientamento, linguaggio, abilità visuospatiali, o dispercezioni).

D. I deficit di cui ai criteri A e C non sono spiegabili sulla base di un preesistente (stazionario o in evoluzione) disturbo neurocognitivo e non si verificano in un contesto di grave riduzione dei livelli di arousal (es coma)

E. Vi è evidenza per storia clinica, esame obiettivo o risultati di laboratorio che il delirium è una diretta conseguenza di un problema clinico, intossicazione o sospensione di farmaci, esposizione a tossine, o è dovuto a molteplici eziologie.

Il delirium è presente se tutti e 5 i criteri sono soddisfatti
<table>
<thead>
<tr>
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<th>Delirium: criteri del DSM-5</th>
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<tbody>
<tr>
<td>A.</td>
<td>Disturbo dell’ attenzione (i.e., ridotta capacità a dirigere, focalizzare, sostenere e shiftare l’ attenzione) e consapevolezza (ridotto orientamento del se nell’ ambiente).</td>
</tr>
<tr>
<td>B.</td>
<td>Il deficit si sviluppa in un periodo di tempo relativamente breve (generalmente ore o pochi giorni ), rappresenta un cambiamento dai livelli di attenzione e consapevolezza di base, e tende a fluttuare in gravità nel corso della giornata.</td>
</tr>
<tr>
<td>C.</td>
<td>É presente un altro deficit cognitivo (es, memoria, disorientamento, linguaggio, abilità visuospaziali, o dispercezioni).</td>
</tr>
<tr>
<td>D.</td>
<td>I deficit di cui ai criteri A e C non sono spiegabili sulla base di un preesistente (stazionario o in evoluzione) disturbo neurocognitivo e non si verificano in un contesto di grave riduzione dei livelli di arousal (es coma)</td>
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<tr>
<td>E.</td>
<td>Vi è evidenza per storia clinica, esame obiettivo o risultati di laboratorio che il delirium è una diretta conseguenza di un problema clinico, intossicazione o sospensione di farmaci, esposizione a tossine, o è dovuto a molteplici eziologie.</td>
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Il delirium è presente se tutti e 5 i criteri sono soddisfatti
Worsening Cognitive Impairment and Neurodegenerative Pathology Progressively Increase Risk for Delirium

Vanta 85+ study, 553 recruited, 4 follow-up waves (3, 5, 8 and 10 yrs) Outcome: any episode of delirium (checklist DSM-III criteria)

Davis DH et al, Am J Ger Psych 2014
DOI: 10.1016/j.jagp.2014.08.005
Acute cognitive impairments induced by LPS are more severe in animals with more advanced neurodegenerative disease.

Davis DH et al, Am J Ger Psych 2014
DOI: 10.1016/j.jagp.2014.08.005
Worsening Cognitive Impairment and Neurodegenerative Pathology Progressively Increase Risk for Delirium

Davis DH et al, Am J Ger Psych 2014
DOI: 10.1016/j.jagp.2014.08.005
Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium

Deborah J. Culley¹*, Mary Snyd¹, Mark G. Baxter², Zhongxiang Xiao⁴, Sharon K. Inouye⁵, Edward R. Marcantonio⁶ and Gregory Crockett⁷

Table 1 | Relevant dimension and positive discriminators used for each stage of the AST.

| Relevant dimension and positive discriminators used for each stage of the AST. |
|----------------------------------|----------------------------------|----------------------------------|
| S+                               | S−                               | Relevant dimension               |
| SD1 Paper vs. Aspen               | Medium                           |
| SD2 Heart vs. Aspen               | Medium                           |
| CD Paper/flower vs. Aspen/triangle | Medium                        |
| CD-R Aspen/flower vs. Aspen/triangle | Medium                  |
| IDS Straw/diamond vs. Cardboard/cross | Medium                      |
| IDS-R Cardboard/diamond vs. Cardboard/cross | Medium                  |
| EDS Wax paper/star vs. Cottar/circle | Shape                           |

Simple discrimination, SD
Compound discrimination, CD
Intradimensional shift, IDS
Extradimensional shift, EDS

10 ratti Fisher (2 anni età) di cui 20 utilizzati per misurazioni citokine
• Iniezione intraperitoneale di LPS
• Test comportamentali AST (sequenza discriminazioni in cui i ratti ricevono un premio nascosto fra 1 di due contenitori (differenti per odore, dimensioni e tessuto) riempiti con materiale di scavo

June 2014 | Volume 6 | Article 107 | 2
FIGURE 1 | Lipopolysaccharide (LPS) produces a robust but transient increase in plasma TNFα and CCL2. Plasma was sampled at the time of sacrifice from aged Fisher 344 rats 2, 24, and 48 h after administration of 50 µg/kg LPS (N = 5 per group) or a control group (N = 5) that received an equal volume of saline intraperitoneally. There was a marked increase in both TNFα (A) and CCL2 (B) 2 h after LPS but the effect resolved completely by 24 or 48 h, respectively. Data are mean ± SEM. ***P < 0.001 by one-way ANOVA.

FIGURE 2 | Lipopolysaccharide (LPS) produces a robust but transient increase in TNFα and CCL2 in the frontal cortex. Rats (N = 5 per group) were treated as described in Figure 1 and frontal cortex harvested at the time of sacrifice. There was no change in TNFα in the frontal cortex at any time compared to control animals (A). CCL2 was elevated nearly threefold above control 2 h after LPS but this resolved by 24 h after treatment (B). Data are mean ± SEM. ***P < 0.001 by one-way ANOVA.
FIGURE 3 | Lipopolysaccharide selectively impaired attention/executive function in aged rats. Twenty-four-month-old Fischer-344 rats ($N = 11$) were tested on two simple discrimination (SD) tasks, one from each dimension (medium and shape) prior to receiving LPS 50 μg/kg or an equal volume of saline i.p. They were tested on the compound discrimination (CD) task and compound discrimination reversal (CD-R) on day 1 after LPS, the intradimensional shift (IDS) and intradimensional shift reversal (IDS-R) on day 2 after LPS, and the extradimensional shift (EDS) on day 3 after LPS. There were no differences between the groups at baseline. LPS did not affect performance on the CD or IDS task but impaired performance on the CD-R and the EDS. This indicates LPS had no effect on simple discrimination learning but did impair attention/executive function for at least 3 days. Data are mean ± SEM. *$P \leq 0.05$, **$P \leq 0.01$ by two-way ANOVA.
Considerazioni

• Iniziali evidenze che uno stimolo infiammatorio-infettivo potente è in grado di indurre in ratti con differente burden neurodegenerativo uno scadimento progressivo (e una fluttuazione delle performances cognitive)
• La severità della compromissione delle performances cognitive è premessa ad un aumentato rischio di delirium
• Iniziali evidenze che uno stimolo infiammatorio-infettivo potente è in grado di indurre in ratti invecchiati un disturbo selettivo dell’attenzione e delle funzioni esecutive
Do anti-inflammatory treatments help?
• NSAID can protect against subsequent development of AD, but these drugs do not appear to be effective when administered to patients with established AD or even as a primary preventative strategy for those at high risk [Vlad, S.C., Neurology 2008].

• NSAID may simply target wrong inflammatory mediators, being primarily directed at inhibition of PG synthesis, though there is evidence that there may be some protection offered by these drugs. Patients already on the cusp of impairment appeared to worsen on treatment with the COX inhibitor naproxen, but those who were not showed significant protection at 2-yr followup [Laino, C., Neurology 2009].

• The timing and consequences of inhibiting brain COXs may be crucial since both isoforms of this enzyme are constitutively expressed and have roles in normal brain function, but inhibiting PGE2 production while the brain still has significant cognitive reserve appears to be beneficial.

• It is of interest that treatment of rheumatoid arthritis patients with anti-TNFα antibodies has been reported to offer very significant protection against the subsequent development of AD [Chou, RC., Am Coll Rheumat 2010].
Statins and Brain Dysfunction: A Hypothesis to Reduce the Burden of Cognitive Impairment in Patients Who Are Critically Ill

Alessandro Morandi, Christopher G. Hughes, Timothy D. Girard, Danny F. McAuley, E. Wesley Ely and Pratik P. Pandharipande

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**Critical Illness**
- Microglial activation (pro-inflammatory phenotype)
  - Apoptotic neuronal loss
    - Injured neurons with degenerating synapses
    - Worse neurological outcomes: ↑ delirium and LTIC

**Statins and Critical Illness**
- Microglial activation (anti-inflammatory phenotype)
  - Apoptotic cell cleaning
    - Synapses stripping from injured neurons
    - Better neurological outcomes: ↓ delirium and LTIC

_Chest_ 2011;140:580-585
DOI 10.1378/chest.10-3065
Una risposta dai traccianti per l’attivazione microgliale?