Commento

Gabriele Tripi

“Delirium: markers biologici e prospettive terapeutiche disease modifying”
Dementia is a challenge for hospitals. Surveys show that around a quarter of hospital beds are occupied by somebody with dementia; a figure which increases in older people and individuals with a superimposed delirium.
Delirium Pathophysiology

Medications
Alcohol withdrawal

Medications
Medical illness
Surgical illness

Benzodiazepine and
Alcohol Withdrawal

Dopamine
Activation

Cholinergic
Activation

Cholinergic
Inhibition

Reduced
GABA Activity

GABA
Activation

Benzodiazepines
Hepatic Failure

Serotonin
Activation

Serotonin
Deficiency

Tryptophan depletion
Phenylalanine elevation

Surgical Illness
Medical Illness

Glucocorticoids
Cushings Syndrome
Surgery
Stroke

Cortisol
Excess

Cytokine Excess

Hepatic failure
Alcohol withdrawal

Periphery: acute insult

- infection
- injury
- surgery (etc.)
- tissue macrophages
  - IL-1β
  - TNF-α
  - IL-6
  - IFNα/β
  - PGE2

activation of LHPA axis, e.g. via CRH in hypothalamus
- GCs

Vulnerable brain: ageing / dementia

- PAMPs
- IL-1β
- TNFα
- IFNα/β
- PGE2
- GCs
- mediators
- primed microglia
  - IL-1β
  - TNFα
  - PGE2

endothelial cells of cerebral vasculature
- GCs
- PGE2
- IL-1RI
- GR
- EP1-4

Acutely impaired neuronal function

damaged neurons

Adrenal cortex

DELIRIUM
Systemic Inflammation Induces Acute Behavioral and Cognitive Changes and Accelerates Neurodegenerative Disease

Colm Cunningham, Suzanne Campion, Katie Lunnan, Carol L. Murray, Jack F.C. Woods, Robert M.J. Deacon, J. Nicholas P. Rawlins, and V. Hugh Perry

Results: Injection of LPS (100 μg/kg), at 12 weeks postinoculation (PI), resulted in heightened CNS interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interferon-beta (IFN-β) transcription and microglial IL-1β translation in prion-diseased animals relative to control animals. This inflammation caused exaggerated impairments in burrowing and locomotor activity, and induced hypothermia and cognitive changes in prion-diseased animals that were absent in LPS-treated control animals. At 15 weeks PI, LPS (500 μg/kg) acutely impaired motor coordination and muscle strength in prion-diseased but not in control animals. After recovery, these animals also showed earlier onset of disease-associated impairments on these parameters.
Abstract

**Background:** Therapeutic use of cytokines can induce delirium, and delirium often occurs during infections associated with elevated levels of cytokines. This study examined the association of demographic, clinical and biological factors (IL-1α, IL-1β, IL-1RA, IL-6, TNF-α, IFN-γ, LIF, IGF-I, APOE genotype) with the presence and severity of delirium.

**Methods:** In an observational prospective longitudinal study, patients aged 70+ were recruited from an elderly medical unit and assessed every 3–4 days (maximum assessments 4). At each time, the scales MMSE, DRS, CAM, APACHEII were administered and blood was withdrawn to estimate the above biological factors. Mixed effects (PQL) and GEE were used to analyse the repeated measurements and investigate the associations at the individual and population average levels.

**Results:** A total of 205 observations on 67 individuals were analysed. Lowest levels of IGF-I, and lower levels of circulating IL-1RA, are significantly ($P < 0.05$) associated with delirium, while the remaining of cytokines, severity of illness and possession of epsilon 4 allele had a non-significant effect. This has been shown by both statistical methods. Similarly lower levels of IGF-I, and high levels of IFN-γ, are statistically significantly ($P < 0.05$) associated with higher DRS scores (more severe delirium).

**Conclusions:** This study finds that (i) low levels of both neuroprotective factors (IGF-I, IL-1RA) are associated with delirium, (ii) high IFN-γ and low IGF-I have significant effects on delirium severity and (iii) otherwise the pro-inflammatory cytokines studied, APOE genotype and severity of illness do not appear to be associated, in older medically ill patients, with either delirium or severity of it.
The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review.

Simone MJ, Tan ZS.

AIMS: To review recent evidence that suggests inflammation plays a similar role in the pathogenesis of delirium and dementia.

METHODS: We performed a literature search of original research and review articles in PubMed using the keywords: delirium, dementia, and inflammation. We summarized the evidence linking inflammation to the pathogenesis of delirium and dementia.

DISCUSSION: Delirium and dementia share similarities in clinical and pathogenic features, leading to the speculation that instead of being distinct clinical entities, the two age-related conditions may be linked by a common pathogenic mechanism. Inflammatory markers have been shown to be elevated in both delirium and dementia, thereby implicating inflammation as a possible mediating factor in their genesis. There is evidence in both basic science and clinical research literature that elevated cytokines play a crucial role in the development of cognitive dysfunction observed in both dementia and delirium.

CONCLUSION: Mounting evidence supports the role of inflammation in the development of both dementia and delirium. Further studies are needed to elucidate the mechanisms underlying these relationships.
Biomarkers for Delirium—A Review

Babar A. Khan, MD, MS, Mohammed Zawahiri, MD, [...], and Malaz A. Boustani, MD, MPH

Abstract

To improve delirium recognition and care, numerous serum biomarkers have been investigated as potential tools for risk stratification, diagnosis, monitoring, and prognostication of delirium. The literature was reviewed, and no evidence was found to support the clinical use of any delirium biomarker, although certain biomarkers such as S-100 beta and insulin-like growth factor-1 and inflammatory markers have shown some promising results that need to be evaluated in future studies with appropriate sample size, prospective designs, and in a more-generalizable population.
## Table 1

Summary of Recent Evidence on the Role of Biomarkers in Delirium

<table>
<thead>
<tr>
<th>Study</th>
<th>Service</th>
<th>Sample Age, Size</th>
<th>Category</th>
<th>Delirium Assessment Tool</th>
<th>Biomarker</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson^16</td>
<td>Medicine</td>
<td>100 84.5 ± 4.2</td>
<td>Risk*</td>
<td>CAM, DSM-III</td>
<td>IGF-1</td>
<td>Low IGF-1 increases the risk of delirium</td>
</tr>
<tr>
<td>Macdonald^18</td>
<td>Medicine</td>
<td>86 82.7 ± 6.6</td>
<td>Risk</td>
<td>CAM</td>
<td>CRP</td>
<td>High levels predict the incidence of delirium</td>
</tr>
<tr>
<td>de Rooij^4</td>
<td>Medicine</td>
<td>185 80</td>
<td>Risk</td>
<td>CAM</td>
<td>Cytokines</td>
<td>Cytokines may contribute to pathogenesis of delirium</td>
</tr>
<tr>
<td>Tagarakis^10</td>
<td>Surgery</td>
<td>154 70.1 ± 7.7</td>
<td>Risk</td>
<td>DRS</td>
<td>ApoE</td>
<td>No correlation between ApoE and postoperative delirium</td>
</tr>
<tr>
<td>Leung^7</td>
<td>Surgery</td>
<td>190 72.5 ± 6</td>
<td>Risk</td>
<td>CAM</td>
<td>ApoE</td>
<td>ApoE carrier status was associated with greater risk of early postoperative delirium</td>
</tr>
<tr>
<td>Van Munster^9</td>
<td>Medicine</td>
<td>264 81.4 ± 76.7</td>
<td>Risk</td>
<td>CAM</td>
<td>ApoE</td>
<td>No evidence that ApoE carriers have higher risk of delirium</td>
</tr>
<tr>
<td>Van Munster^16</td>
<td>Surgery</td>
<td>98 84.6 ± 7.1</td>
<td>Risk</td>
<td>CAM, DOS, DRS-R-98</td>
<td>Cytokines</td>
<td>Patients with postoperative delirium have higher levels of IL-6 and IL-8</td>
</tr>
<tr>
<td>Lemstra^22</td>
<td>Surgery</td>
<td>68 78.5 ± 80</td>
<td>Risk</td>
<td>DSM-IV, CAM, DRS-R-98, Digit Span Test</td>
<td>CRP, IL-6, IGF-1</td>
<td>No correlation found between preoperative inflammatory markers levels and postoperative delirium</td>
</tr>
<tr>
<td>Van Munster^8</td>
<td>Medicine, surgery</td>
<td>656 77.4 ± 7.8</td>
<td>Risk</td>
<td>CAM, DOS</td>
<td>ApoE</td>
<td>Delirium associated with presence of ApoE-4 allele</td>
</tr>
<tr>
<td>Van Munster^13</td>
<td>Surgery</td>
<td>120 84.8 ± 6.9</td>
<td>Risk, diagnosis</td>
<td>CAM, DOS</td>
<td>Cortisol, IL, S-100 β</td>
<td>Cortisol, IL-6, and S-100 β may have a role in the pathogenesis of delirium. S-100 β is the strongest independent marker</td>
</tr>
<tr>
<td>Author</td>
<td>Setting</td>
<td>Study Measurements</td>
<td>Case Mix</td>
<td>Additional Variables</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>--------------------</td>
<td>----------</td>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Adamis11</td>
<td>Medicine</td>
<td>164 84.6 ± 6.57 Risk, CAM, DRS</td>
<td>ApoE, Cytokines</td>
<td>Relationship between ApoE, low IGF-1, and delirium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ely12</td>
<td>ICU</td>
<td>53 53.2 ± 21.9 Risk, CAM-ICU</td>
<td>ApoE</td>
<td>Presence of ApoE significantly associated with a longer duration of delirium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adamis15</td>
<td>Medicine</td>
<td>67 84.2 ± 6.3 Risk, CAM, DRS</td>
<td>Cytokines, IGF-1, ApoE</td>
<td>Low levels of IGF-I associated with delirium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas18</td>
<td>Medicine</td>
<td>61 86.2 ± 4.5 Diagnosis CAM, Delirium Index</td>
<td>SAA</td>
<td>SAA levels did not correlate with electroencephalographic parameters in diagnosing delirium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Munster23</td>
<td>Medicine</td>
<td>412 81.6 ± 7.9 Diagnosis CAM, DOS, DRS-R-98</td>
<td>S-100 β</td>
<td>Higher levels of S-100 β were found in patients with delirium than in those without</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Munster24</td>
<td>Surgery</td>
<td>120 84.8 ± 6.9 Diagnosis CAM, DOS, DRS-R-98</td>
<td>S-100 β, NSE</td>
<td>Delirium associated with high levels of S-100 β but not with NSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaschke21</td>
<td>ICU</td>
<td>114 73.3 ± 6.0 Diagnosis CAM-ICU</td>
<td>Cortisol, IL-6</td>
<td>Early postoperative delirium after cardiac surgery associated with higher cortisol and IL-6 levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Markers genetici

• **Apo-E4** allele was associated with longer delirium duration (OR = 7.32), but the CI was extremely wide (1.82–29.51).

• The median duration of delirium was **4 days** for patients with an **Apo-E4** allele and **2 days** for patients without.
Mediatori infiammatori

• Highest levels of Cortisol (666 nmol/L, 95% CI = 475–859 nmol/L) were found before delirium onset
• In a medical population, high CRP levels predicted delirium incidence after adjusting for other covariates (P = .02).
• These findings raise the possibility of CRP, and cortisol as predictive markers of delirium and incorporating them into a clinical tool to better predict delirium onset.
IGF-1

- Low levels of IGF-1 can predispose to delirium and may increase its severity
- Low baseline IGF-1 levels on admission were associated with greater risk of incident delirium.
- Low IGF-1 levels in older medical patients were shown to be associated with delirium (P = .02)
- High IGF-1 levels were associated with low Delirium Rating Scale (DRS) scores.
- Delirium was significantly associated with a previous history of dementia, older age, greater illness severity, disability, and low IGF-1 level
Markers di intensità

- Astrocytes mainly express S-100 β, and high levels may indicate indirect injury to glial cells in delirium
- A strong association between S-100 β and delirium has been demonstrated
- There is high S-100 β levels in individuals with delirium
- There is, probably, correlation between S-100 β and the proinflammatory cytokines IL-6 and IL-8, hinting at the complex relationship between inflammation and possible cerebral damage.
Markers infiammatori

- All studies documented significant associations between IL-6 and IL-8 and delirium.
- After adjusting for age, cognitive impairment, and infection, having IL-6 and IL-8 levels above the detection limits was significantly associated with delirium.
Attività anticolinergica serica

- No significant differences in SAA levels between individuals with and without delirium were found.
- SAA levels did not correlate with any electroencephalographic parameters considered to be criterion standards of delirium Diagnosis.
- SAA may reflect peripheral anticholinergic activity, which in turn does not translate into central cholinergic deficiency resulting in delirium.
Conclusioni

• La letteratura attuale definisce il ruolo dell’Apo-E4 allele come risk factor per l’insorgenza di delirium e per una più lunga durata di questo.

• Più elevati livelli di Cortisolo e PCR possono predire l’insorgenza di delirium, soprattutto se associati a bassi livelli di IGF-1.

• L’utilizzo della Attività dell’Acetilcolina Serica (SAA) per riflettere l’attività colinergica centrale non è stata dimostrata negli studi inclusi in questa review.
Conclusioni

- Il Delirium può essere visto anche come lo sviluppo di un disturbo del comportamento cui contribuiscono significativamente le citochine infiammatorie.
- Le citochine, causando sintomi come la febbre, la stanchezza, la sonnolenza, determinano difficoltà di concentrazione, disturbi del sonno, agitazione, che sono alcuni dei sintomi cardinali del delirium.
Le citochine possono indurre una riduzione dell’attività colinergica, specialmente negli anziani con sottostanti processi degenerativi come la Demenza di Alzheimer.

Questo può determinare, a sua volta, un circolo vizioso di inadeguata regolazione dell’infiammazione dovuta alla deplezione colinergica.

Conclusioni
Conclusioni

• L’utilizzo appropriato di biomarkers potrebbe contribuire ad una migliore definizione del delirium ed una capacità predittiva della sua storia naturale.

• L’identificazione di biomarkers significativi nel campo del delirium non aiuterà solo a comprendere meglio la complessa patofisiologia, ma traccerà la strada per lo sviluppo di nuove interventi “disease modifying”
...interactions among IL-1β, GABA and ACh are of considerable interest for delirium and require detailed further study. Microglia primed by primary pathology to produce exaggerated IL-1β responses to subsequent inflammatory stimulation were implicated in the acute cognitive deficits in both of these studies.
Delirium in elderly people: a review

Sónia Martins¹ and Lia Fernandes¹,²,³ *

¹ Research and Education Unit on Aging, UNIFAVA/ICBAS, University of Porto, Porto, Portugal
² Clinical Neuroscience and Mental Health Department, Faculty of Medicine, University of Porto, Porto, Portugal
³ Psychiatry Service, S. João Hospital, Porto, Portugal

The present review aims to highlight this intricate syndrome, regarding diagnosis, pathophysiology, etiology, prevention, and management in elderly people. The diagnosis of delirium is based on clinical observations, cognitive assessment, physical, and neurological examination. Clinically, delirium occurs in hyperactive, hypoactive, or mixed forms, based on psychomotor behavior. As an acute confusional state, it is characterized by a rapid onset of symptoms, fluctuating course and an altered level of consciousness, global disturbance of cognition or perceptual abnormalities, and evidence of a physical cause. Although pathophysiological mechanisms of delirium remain unclear, current evidence suggests that disruption of neurotransmission, inflammation, or acute stress responses might all contribute to the development of this ailment. It usually occurs as a result of a complex interaction of multiple risk factors, such as cognitive impairment/dementia and current medical or surgical disorder. Despite all of the above, delirium is frequently under-recognized and often misdiagnosed by health professionals. In particular, this happens due to its fluctuating nature, its overlap with dementia and the scarcity of routine formal cognitive assessment in general hospitals. It is also associated with multiple adverse outcomes that have been well documented, such as increased hospital stay, function/cognitive decline, institutionalization and mortality. In this context, the early identification of delirium is essential. Timely and optimal management of people with delirium should be performed with identification of any possible underlying causes, dealing with a suitable care environment and improving education of health professionals. All these can be important factors, which contribute to a decrease in adverse outcomes associated with delirium.
Un incremento prostaglandinico con maggiore espressività di COX1 da parte della microglia è indispensabile, ma non sufficiente a determinare peggioramento delle condizioni cognitive, tuttavia, quando attivato da altri fattori infiammatori, tipo IL1 Beta, si determina l'impairment cognitivo.
Figure 3. Effects of subchronic nimesulide and ibuprofen administration on spatial memory performance. 3A: choice accuracy (Entries to repeat; ETR) (Data are presented as mean ± SEM). 3B: response latency (RL) (Data are presented as mean ± SEM). ** expresses the statistically significant value (p <0.01).
NEW HORIZONS

New horizons in the pathogenesis, assessment and management of delirium

Alasdair M. J. MacLullich\textsuperscript{1,2}, Atul Anand\textsuperscript{1}, Daniel H. J. Davis\textsuperscript{2,3}, Thomas Jackson\textsuperscript{4}, Amanda J. Barugh\textsuperscript{1,2}, Roanna J. Hall\textsuperscript{1,2}, Karen J. Ferguson\textsuperscript{1,2}, David J. Meagher\textsuperscript{5}, Colm Cunningham\textsuperscript{6}

\textsuperscript{1}Edinburgh Delirium Research Group, Geriatric Medicine Unit, University of Edinburgh, Room S1642, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, UK
\textsuperscript{2}Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
\textsuperscript{3}Department of Public Health and Primary Care, University of Cambridge, UK
\textsuperscript{4}School of Immunity and Infection, University of Birmingham, Birmingham, UK
\textsuperscript{5}University of Limerick Medical School, Limerick, Ireland
\textsuperscript{6}Trinity College Institute of Neuroscience and School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland

Address correspondence to: A. M. J. MacLullich. Tel: (+44) 1312426481; Fax: (+44) 1312426370. Email: a.maclullich@ed.ac.uk
A. M. J. MacLullich et al.

Key points

- Delirium is one of the major unmet medical needs in modern clinical practice.
- Delirium strongly predicts future new-onset dementia and accelerates existing dementia.
- Delirium prevention is effective but implementation in clinical practice is still lacking.
- Animal model research has provided valuable insights into possible mechanisms.
- Higher detection rates of delirium in routine practice remains a major priority.
Preoperatively high neopterin levels predicted delirium after cardiac surgery in older adults, in addition to the well-known risk factors of poor cognitive function, high cardio-surgical risk, and combined CABG and valve surgery. Postoperative neopterin and HVA levels were also found to be associated with delirium, together with preoperative cognitive functioning. Plasma neopterin may be a candidate biomarker for delirium after cardiac surgery in these older adults.
Grazie dell’attenzione