Systemic inflammation and delirium during critical illness

Nathan E. Brummel et al, Intensive Care Med (2024)

RESEARCH AIM

To investigate the association between markers of inflammation and endogenous anticoagulant activity with delirium and coma in critically ill patients

BACKGROUND

- Up to half of all critically ill patients are affected by delirium.
- Acute inflammation and a reduction in endogenous anticoagulant activity are hypothesized to contribute to the development of delirium during critical illness.
- Previous studies were characterized by low sample size and inconsistent findings
- The mechanism contributing to delirium and coma in the critical ill patient is still unknown.

METHODS

Design: Prospective, multicentric, cohort study including 5 centres in the USA.

Population: Adult patients ≥18 years of age with respiratory failure and/or shock in a medical or surgical ICU.

Exposure: CRP, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, MMP-9, TNF-α, TNFR1 and protein C measured at day of admission (day 1), day 3 and day 5.

Outcome parameters:
1) Occurrence of:
- Delirium (RASS -3 or greater and a positive CAM-ICU)
- Coma (RASS -4 or -5).

the day following measurements of markers.

2) Delirium/ coma-free days during the 7 days after marker measurement.

Covariates: Age, severe sepsis, modified SOFA score, study day, steroids, mean 24-h doses of sedatives and opiates

Statistic: Multivariable regression analysis adjusted for covariates and proportional odds logistic regression.

RESULTS

- 991 patients were enrolled between January 2007 and December 2010. Incidence of delirium was 70% in the 11 days following enrolment with a median duration of 3 (IQR 2-5) days.
- Delirium was present in 35%, 29%, and 22%, and coma in 27%, 17%, and 12% on days 2, 4, and 6, respectively.
- Biomarkers associated with delirium or coma:

Markers	Delirium		Coma		Delirium / coma-free days	
	Delirium OR (95%CI)	p	Delirium OR (95%CI)	p	Delirium OR (95%CI)	p
CRP	1 (0.8-1.2)	0.11	**1.4 (1.1-1.7)**	**0.02**	0.9 (0.7-1.0)	0.68
IFN-γ	1.1 (1-1.3)	0.21	**1.3 (1.1-1.6)**	**0.02**	0.9 (0.8-1.0)	0.12
IL-6	**1.8 (1.5-2.3)**	**<0.001**	**2.3 (1.8-3.0)**	**<0.001**	**0.6 (0.5-0.7)**	**<0.001**
IL-8	**1.3 (1.1-1.5)**	**0.03**	**1.8 (1.4-2.3)**	**<0.001**	**0.7 (0.6-0-8)**	**<0.001**
IL-10	**1.5 (1.2-1.8)**	**<0.001**	**1.5 (1.2-2.0)**	**0.005**	**0.7 (0.6-0.8)**	**<0.001**
TNF-α	**1.2 (1.0-1.4)**	**0.04**	1.2 (1.0-1.5)	0.14	1 (0.8-1.1)	0.47
TNFR1	**1.3 (1.1-1.6)**	**0.01**	1.2 (0.9-1.5)	0.39	0.8 (0.7-1.0)	0.21
Protein C	**0.7 (0.6-0.8)**	**<0.01**	**0.6 (0.5-0.9)**	**<0.001**	**1.3 (1.1-1.5)**	**0.008**

SIS COMMENTS

This study explored biomarkers of systemic inflammation related to qualitative and quantitative changes in consciousness levels in patients with respiratory failure and shock, identifying factors potential associated with the pathophysiology of delirium and coma in the critical care setting.

Delirium is a common complication in critical care and has been the subject of extensive research. A major challenge with this often underrecognized condition is the absence of specific treatments, largely due to limited understanding of the pathophysiological mechanisms that lead to these abrupt changes in cognitive and alertness functions, without corresponding findings in brain imaging or classical spinal fluid analysis. Factors such as metabolic disturbances, neurotransmitter imbalances, alterations in melatonin production and inflammatory processes have been suggested as potential contributors. Proteomic analyses of blood and cerebrospinal fluid over the past decades have underscored the role of systemic and compartmental inflammation in delirium development.[2]

The research conducted by Brummel and colleagues, which examined the inflammatory patterns in blood samples from nearly 1,000 patients across five centres, further supports the significance of inflammatory markers as potential pathophysiological mediators.[3]
Notably, this investigation is one of the largest of its kind and provides insights into the emerging topic of longitudinal measurement of inflammatory parameters to identify related diseases. Early inflammatory cytokines, such as IL-6 or TNF-α, exhibit rapid kinetics, often confounding the investigation of the association with the clinical picture due to delayed presentation. Thus, it has been suggested that repeated monitoring of these markers could improve the prediction of clinical outcome paraemters.[4]

Further investigation into the dynamic trajectories of inflammatory markers may clarify their relationship with an altered mental status such as delirium and coma, potentially revealing therapeutic targets to treat delirium in patients with systemic inflammatory conditions.

1. Wilson et al. Delirium. Nature Reviews Disease Primers, 2020.
2. Poljak et al. Quantitative proteomics of delirium cerebrospinal fluid. Intensive Care Medicine, 2014.
3. Brummel et al. Systemic inflammation and delirium during critical illness. Intensive Care Medicine, 2024.
4. Tong-Minh et al. Joint Modeling of Repeated Measurements of Different Biomarkers Predicts Mortality in COVID-19 Patients in the Intensive Care Unit. Biomarker Insights, 2022.