High cortisol levels are associated with brain dysfunction but low prolactin cortisol ratio levels are associated with nosocomial infection in severe sepsis

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Brain dysfunction in the ICU

Coma and delirium

Increase ICU morbidities
Nosocomial infection
Prolonged MV length

Increase ICU length of stay

Independent risk factor of ICU mortality

Ely W, JAMA 2004
Lin SM, J Crit Care 2008
Vincent JL, Lancet 2003
Brain dysfunction in the ICU

Up to 70% of ICU patients and multifactorial
- Hypotension
- Hypoxia
- Excessive brain inflammation
- Aging with previous brain degenerative disorders
- Sedatives and anesthesia administration
- Harmful excessive stress hormones release (cortisol)

Sonneville R et al. Ann Intensive Care 2013
Excessive stress hormone release is harmful for the brain

- Cortisol as biomarker of delirium in acute coronary syndrome, stroke, Cushing’s disease, after cardiac surgery, and in elderly after hip fracture
  
  *Marklund N, J Intern Med 2006*
  *Mu DL, Crit Care 2010*
  *Michaud K, J Neurosci 2010*
  *van Munster BC, Brain Cognition 2010*

- In sepsis, high cortisol levels are observed in:
  
  Non-survivors from septic shock
  
  *Annane D, JAMA 2002*
  
  In a small number of fatal septic patients who developed delirium.
  
  *Pfitser D, Crit Care 2008*

- Immunosuppressive and inflammatory effect
Excessive stress hormone release is harmful for the brain

- High prolactin levels in neuropsychiatric disorders (Schizophrenia, mood alteration, bipolar disorder)
  
  Sobrinho LG, Baillieres Clin Endocrinol Metab 1991  
  Fava M, Psychother Psychosom 1983  
  Kellner R, Am J Psychiatry 1984

- In sepsis, low prolactin levels are observed are frequent in pediatric patients with sepsis
  
  Heidermann R, Pediatric Crit Care Med 2013

  Higher incidence of nosocomial infection
  
  Felmet KA, J Immunol 2005

- Immunostimulating effect: low levels reduce T-lymphocyte function in rats and increase their mortality in sepsis
  
  Bernton EW, Science 1988  
Aim of the study

Investigate the impact of stress hormone cortisol and prolactin levels on the development of brain dysfunction and nosocomial infection in patients with severe sepsis and septic shock
Exclusion criteria

- Age < 18
- Pregnancy
- Advanced malignancy
- Non-survivors in the first 24 hours in the ICU
- Concomittant treatment: cortisol, dopamine, levodopa, bromocriptine, haloperidol, metoclopramide, antipsychotic drugs
- Cardiorespiratory arrest
- Post-neurosurgical patients or hypophysectomy
- Brain disorders: meningitis, trauma, bleeding, stroke, seizures, Parkinson,
- Dementia, disabled neuromuscular or severe psychiatric disorders
- Liver cirrhosis
- Terminal kidney failure
- Severe hypothyroidism
- Addison
- Alcohol withdrawal
- Macroprolactin
Brain dysfunction assessment

- Glasgow Coma Scale < 13 at admission
- Richmond Agitation Sedation Scale (RASS) score
- Confusion Assessment Method in the ICU (CAM-ICU) 
  \[Ely \ W \ et \ al. \ JAMA \ 2004\]

24 hours after sedation withdrawal
- Delirium if RASS > -3 and CAM-ICU positive for at least 2 consecutive days
- Coma if RASS ≤ -4 or throughout ICU stay
Brain dysfunction after 24 H sedation withdrawal

127 patients with severe sepsis and septic shock

Brain dysfunction
107 (84%)

85 delirium (80%)  22 coma (20%)

82/107 patients after first sepsis (77%)

62/82 documented nosocomial infection (76%)
### RESULTS

<table>
<thead>
<tr>
<th>Characteristics at ICU admission and comorbidities</th>
<th>n = 127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65 ± 14</td>
</tr>
<tr>
<td>APACHE score</td>
<td>83 ± 30</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>208 ± 129</td>
</tr>
<tr>
<td>Males / females, n (%)</td>
<td>83/45 (65/35)</td>
</tr>
<tr>
<td>Medical / surgical patients, n (%)</td>
<td>106/22 (83/17)</td>
</tr>
<tr>
<td>Bronchopneumonia, n (%)</td>
<td>93 (73)</td>
</tr>
<tr>
<td>Peritonitis, n (%)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Gram negative / positive, n (%)</td>
<td>65/42 (51/49)</td>
</tr>
<tr>
<td>Active smoking, n (%)</td>
<td>33 (26)</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30), n (%)</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>53 (42)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Alcohol abuse, n (%)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>History of brain disorder, n (%)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>History of Sepsis, n (%)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>ICU evolution</td>
<td>All patients (n=127)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Cortisol admission (nmol/L)</td>
<td>413 ± 757</td>
</tr>
<tr>
<td>Prolactin admission (pmol/L)</td>
<td>802 ± 824</td>
</tr>
<tr>
<td>Mechanical ventilation, days</td>
<td>16 ± 14</td>
</tr>
<tr>
<td>Inotropics length, days</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>Sedation, days</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>Midazolam, n (%)</td>
<td>80 (62)</td>
</tr>
<tr>
<td>Fentanyl, n (%)</td>
<td>75 (59)</td>
</tr>
<tr>
<td>Propofol, n (%)</td>
<td>48 (37)</td>
</tr>
<tr>
<td>Nosocomial infection, n (%)</td>
<td>67 (52)</td>
</tr>
<tr>
<td>Shock recurrence, n (%)</td>
<td>37 (29)</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>69 (54)</td>
</tr>
</tbody>
</table>
Cortisol levels over the first four days after ICU admission

Brain dysfunction

No brain dysfunction

p = 0.007
Prolactin levels over the first four days after ICU admission

Brain dysfunction

No brain dysfunction

p = 0.071
Cortisol prolactin ratio over the first four days after ICU admission

Brain dysfunction

No brain dysfunction

p = 0.568
Prolactin levels over the first four days after ICU admission

\[ p = 0.019 \]
Cortisol prolactin ratio over the first four days after ICU admission

p = 0.012

No nosocomial infection

Nosocomial infection
Cortisol prolactin ratio over the first four days after ICU admission

Males

Females

p = 0.675
SOFA score over the first four days after ICU admission

Brain dysfunction

No brain dysfunction

p = 0.022
## Logistic regression results

<table>
<thead>
<tr>
<th>Covariates brain dysfunction</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA score admission</td>
<td>1.17</td>
<td>1.06, 1.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Cortisol</td>
<td>1.92</td>
<td>1.32, 1.71</td>
<td>0.021</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates nosocomial infection</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin/cortisol ratio</td>
<td>1.03</td>
<td>1.01, 1.13</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Cortisol and brain dysfunction

Cortisol

Blood brain barrier leakage

Inhibition glucose uptake and utilisation

Brain hippocampus frontal cortex

ATP depletion

Accumulation toxic radicals, glutamate

Salpolsky, J Neurosci 1985
Salpolsky, J Neurosci 1986
Stress hormone and nosocomial infection

Sepsis, inflammation, stress

prolactin↑

Immunostimulating
Stimulating T-lymphocytes function

Bernton EW, Science 1988

Bernton EW, Science 1988

cortisol↑

Immunosuppressive
Reduces T-lymphocytes function

Chrousos GP, NEJM 1995
Webster JL, J Endocrinol 2004
Conclusions

• High cortisol levels are associated with the development of brain dysfunction in severe sepsis
• Low prolactin/cortisol ratio are associated with higher risk of development of nosocomial infection,