Journal of Critical Care 33 (2016) 56–61

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Sepsis/Infection

High prolactin levels are associated with more delirium in septic patients

Duc Nam Nguyen, MD [a,*], Luc Huyghens, MD, PhD [a], Johan Schiettecatte [b], Johan Smitz, MD, PhD [b], Jean-Louis Vincent, MD, PhD [c]

[a] Department of Critical Care Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit of Brussel, Brussels, Belgium
[b] Laboratory of Clinical Chemistry & Radioimmunology, Universitair Ziekenhuis Brussel, Vrije Universiteit of Brussel, Brussels, Belgium
[c] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

ARTICLE INFO

Keywords:
Prolactin
Delirium
SOFA score
Nosocomial infections
Aging

ABSTRACT

Purposes: We investigated whether high prolactin levels were associated with delirium in septic patients because neuropsychiatric disorders are frequently associated with hyperprolactinemia.
Materials and methods: Prolactin levels were measured daily for 4 days in 101 patients with sepsis. Delirium was assessed using the Richmond Agitation Sedation Scale and the Confusion Assessment Method in the ICU.
Results: Delirium developed in 79 patients (78%) and was more common in patients older than 65 years. Prolactin levels were higher in patients with delirium than in those without over the 4 days of observation ($P = .032$). In patients with delirium, higher prolactin levels were associated with a lower incidence of nosocomial infection ($P = .006$). Multivariable logistic regression showed that the Sequential Organ Failure Assessment score at intensive care unit admission (odds ratio, 1.24; 95% confidence interval, 1.04-1.48; $P = .002$) and the combined effect of prolactin levels with age (odds ratio, 1.018; 95% confidence interval, 1.01-1.031; $P = .006$) were associated with the development of delirium.
Conclusions: High prolactin levels may be a risk factor for delirium in septic patients.

1. Introduction

Although vital for stimulating cognitive function, motor reflexes, and immunity for host survival, stress activation of the hypothalamic-pituitary-adrenal axis (HPA) is commonly disturbed in sepsis [1]. The resultant aberrant stress hormone responses, including those of cortisol, catecholamines, and prolactin, may be deleterious for the brain and the immune system where their specific receptors are abundant [2,3].

Aberrant stress hormone response and disturbance of the neurotransmission system (including dopamine hyperactivity, and cholinergic and serotoninergic deficiency) working in concert with hypotension, hypoxia, and excessive brain inflammation are important risk factors in the pathogenesis of cognitive dysfunction or delirium in critical illness [4,5]. It has been reported that excessive stress cortisol release is immunosuppressive and involved in the development of delirium in sepsis, in psychosis, and in Cushing disease [6–8].

Similar to cortisol, prolactin is a stress hormone that can affect behavioral or cognitive function and is involved in the regulation of the immune system, beyond its sexual reproductive and lactogenesis properties [9,10]. Hyperprolactinemia has frequently been reported in neuropsychiatric disorders, including schizophrenia, bipolar disorder, and altered mood [11–14]. It has been also shown that prolactin can have a harmful effect on the brain in experimental studies. In vitro, prolactin can stimulate cytokine release from astrocytes [15]. In rats, prolactin administration can induce a thrombogenic effect and aggravate brain endothelial dysfunction when it passes into the brain [16]. However, unlike cortisol, it is not known whether stress-induced prolactin release has any impact on the brain and cognitive function in clinical sepsis.

In this prospective observational study, we investigated the association between prolactin levels and cognitive function in septic patients. We hypothesized that excessive stress-induced prolactin release may be associated with delirium.

2. Materials and methods

The study was conducted in a 24-bed multidisciplinary, mixed medical-surgical department of intensive care in a university teaching hospital. The Ethical Committee of our hospital approved the study, and informed consent was obtained from the patients' relatives and from the control patients.

2.1. Subjects

All patients admitted to the intensive care unit (ICU) between May 2010 and September 2012 with a diagnosis of sepsis or septic shock as defined according to standard criteria [17] were considered for

* Corresponding author at: Department of Critical Care Medicine, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, Brussels 1090, Belgium. Tel.: +32 24775178; fax: +32 24775179.
E-mail address: namduc.nguyen@uzbrussel.be (D.N. Nguyen).

http://dx.doi.org/10.1016/j.jcrc.2015.12.021
0883-9441/

inclusion. Exclusion criteria included the following: patients younger than 18 years of age, concomitant treatment interfering with prolactin release (dopamine, levodopa, bromocriptine, metoclopramide, haloperidol, tricyclic antidepressant, antipsychotic drugs), pregnancy, cerebral disorder (prolactinoma, seizures, trauma, stroke, hemorrhage, meningitis, posthypophysectomy or other neurosurgery), post–cardiorespiratory arrest, alcohol withdrawal, psychiatric disorder, dementia, disabling neuromuscular disorders, Parkinson disease, severe hypothyroidism, advanced liver cirrhosis, chronic kidney hemodialysis, and advanced malignancy. We also excluded patients who died in the first 24 hours after the onset of sepsis.

A control group of 40 age-matched, nonseptic patients on the general ward (surgical and medical) who had no organ dysfunction and none of the exclusion criteria was also selected.

Sepsis management was conducted according to international consensus guidelines [17]. A mean arterial pressure greater than or equal to 65 mm Hg was targeted using fluid administration and norepinephrine (up to 1 μg/[kg min]). Dobutamine (at doses up to 10 μg/[kg min]) was added if indicated. Mechanical ventilation targeted a tidal volume of 6 to 7 mL/kg ideal body and a plateau pressure less than 30 cm H_2O.

In patients receiving mechanical ventilation, sedation was initially started using midazolam (up to 0.05 mg/[kg h]) or propofol (up to 4 mg/[kg h]), and analgesia was achieved using fentanyl (up to 0.05 mg/[kg min]) or remifentanil (up to 0.75 μg/[kg h]). The doses of these agents were adapted daily to obtain a Richmond Agitation Sedation Scale (RASS) score [18] between 0 and −3. The physician in charge of the patient decided when to withdraw sedation and when to wean from mechanical ventilation.

Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) III score, and organ dysfunction was assessed on admission and daily thereafter using the Sequential Organ Failure Assessment (SOFA) score. *Nosocomial infection* was defined as a newly documented episode of sepsis occurring 72 hours after ICU admission, which was associated with a positive microbiological culture or a new lung infiltrate on the chest radiograph and needed a change in antibiotic therapy [19]. A patient who developed shock in association with nosocomial infection was said to have recurrent septic shock.

2.2. Serum prolactin measurements

Serum prolactin concentrations were measured between 6 and 12 hours after ICU admission and then once daily in the morning for the next 3 days. Prolactin was also measured daily in the control patients for 4 days. Prolactin was measured using the Elecsys prolactin II assay on a Cobas 6000 instrument (Roche Diagnostics, Mannheim, Germany) with a within-run coefficient of variation less than 3% and a between-run coefficient of variation less than 4% (range, 266-13 896 pmol/L). Normal values in our laboratory are 176 to 797 pmol/L for males and 147 to 1044 pmol/L for females. The polyethylene glycol precipitation test was used to detect macroprolactin in all blood samples with a prolactin concentration greater than 2043 pmol/L [20]. Blood samples with a prolactin recovery after polyethylene glycol precipitation of less than 40% (the percentage that contained ≥60% of macroprolactin) were excluded from the analysis.

2.3. Delirium assessment and treatment

From ICU admission until ICU discharge, the Confusion Assessment Method in the ICU (CAM-ICU) and the RASS were assessed twice daily by the nurse or physician in charge of the patient, who was not aware of the prolactin results. In sedated patients, CAM-ICU assessment was started 24 hours after sedation withdrawal. A diagnosis of delirium was considered when the RASS score was greater than −3 and the CAM-ICU was positive for at least 2 consecutive days. When a positive CAM-ICU was combined with a RASS score of −2 to −1, the patients were said to have hypoactive delirium, and when combined with a RASS score of 1 to 5, they were classified as having hyperactive delirium. The presence of delirium was evaluated at times when the patient was not undergoing any stressful event (physiotherapy, weaning from mechanical ventilation, or any medical invasive procedure) to avoid an effect on prolactin release and a false-positive CAM-ICU result. When indicated, the physician in charge of the patient performed brain computed tomography in patients with delirium to exclude stroke or hemorrhage.

Hyperactive delirium was treated with an antipsychotic drug (haloperidol or dehydrobenzperidol), an α2-receptor agonist (clonidine or dexmedetomidine), or both. All sedative agents were avoided in hypoactive delirium. Nonpharmacological therapies of delirium, including early mobilization and prevention of sleep deprivation, were used in all patients.

2.4. Statistical analysis

The statistical analysis was performed with SPSS version 21.0 (SPSS, Chicago, IL). A χ^2 test or Fisher exact test was used for comparisons of categorical variables when appropriate. Continuous variables underwent logarithmic transformation to assume a normal distribution. Analysis of variance for repeated measures with Bonferroni test for post hoc comparisons adjusting for age and sex or a Student *t* test was used for comparisons between groups. The correlation between continuous variables was evaluated with the Pearson or Spearman correlation test when appropriate.

A multivariable binary logistic regression model adjusted with stepwise selection of covariates (prolactin levels at admission, C-reactive protein [CRP] levels at admission, age, sex, the admission SOFA score, the duration of sedation, the administration of midazolam and fentanyl as binary variable, and one interaction term: age × prolactin levels at admission) was used to determine the risk factors associated with the development of delirium. The model was selected based on Akaike criterion values. Variables with a univariate logistic regression χ^2 *P* value < .2 were added and retained in the multivariable model at *P* values ≤ .05. The receiver operating characteristic curve and the area under the curve were calculated for the logistic regression model and to determine the cutoff value of prolactin associated with delirium.

Statistical significance was considered at a 2-sided *P* value < .05.

3. Results

3.1. Patient characteristics

A total of 150 consecutive septic patients were enrolled in the study. Forty-nine patients were excluded, including those who died without proper neurological and cognitive evaluation under sedation, so that 101 patients were included in the analysis (Fig. 1). Of these 101 patients, 98 patients (97%) were sedated and receiving mechanical ventilation, and 79 (78%) developed delirium: hyperactive in 40 (51%) and hypoactive in 39 (50%). The median duration of delirium was 6 (4-12) days. Brain computed tomography detected stroke or hemorrhage in 5 (all hypoactive) of 18 delirious patients.

The patients' characteristics are shown in Table 1. Patients who developed delirium were older (66 ± 13 vs 59 ± 17, $P = .047$) and had higher APACHE III scores (85 ± 29 vs 67 ± 24, $P = .018$) than patients without delirium.

During the ICU stay, patients with delirium were more likely to develop nosocomial infection and recurrence of septic shock than those without delirium. They also more frequently developed critical illness polyneuromyopathy, had longer ICU stays, and had higher ICU mortality rates (Table 2).