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C-reactive protein and procalcitonin levels may not predict delirium in critically ill children

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Abstract

Objectives: The objective of this study was to investigate the relationship between C-reactive protein (CRP) and procalcitonin and the diagnosis of delirium in critically ill children.

Design: Retrospective cohort study

Setting: Tertiary care urban academic Pediatric Intensive Care Unit (PICU)

Patients: All PICU patients (ages 0–21 years) admitted between January 1, 2015 and December 31, 2017, who had a CRP and/or procalcitonin level drawn within the first 14 days of their PICU stay.

Intervention: None

Measurements and Main Results: Each patient was screened for delirium and/or coma twice daily using the Cornell Assessment of Pediatric Delirium. Patient information including demographics, delirium status, and lab values were extracted from the electronic medical record. 734 patients were enrolled, with CRP and procalcitonin levels drawn in 664 and 587 patients respectively. 37% (n=274) of patients were delirious on at least one study day. In bivariate analysis, CRP was not related to either delirium or coma. Procalcitonin was highest on days with coma and lowest on days with delirium. There was no statistically significant relationship between inflammatory markers and any subtype of delirium.

Conclusions: Despite evidence of inflammatory markers being predictive of delirium in adults, in this retrospective pediatric cohort, no association was found between CRP or procalcitonin levels and development of delirium.

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Keywords

delirium; pediatric; inflammation; C-reactive protein (CRP); procalcitonin; biomarker

Introduction

Delirium has been defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-V) as an altered mental state characterized by acute onset, a fluctuating course, and a disturbance of awareness and cognition (1). It is a frequent hospital-acquired complication in critically ill children, known to affect up to 25% of the patients admitted to the pediatric intensive care unit (PICU) (2). Risk factors for the development of delirium in children can be divided into non-modifiable (younger age, neurodevelopmental delay, invasive mechanical ventilation, higher severity of illness) and potentially modifiable (benzodiazepine use, use of physical restraints, red blood cell transfusion) (2–5). In the population of critically ill children, delirium has been associated with a near-doubling of PICU and hospital length of stay, increased morbidity, increased in-hospital mortality, and increased hospital costs (2,3,6). Given that delirium is associated with deleterious outcomes in children, it is essential that we investigate the pathophysiology underlying the development of pediatric delirium.

Several hypotheses for the pathogenesis of delirium have been proposed, including inflammation, oxidative stress, neuroendocrine abnormalities, and diurnal dysregulation (7). In adults, several studies have shown a relationship between systemic inflammatory markers (CRP, procalcitonin, IL-6, IL-8, TNF-alpha, S-100 Beta) and the development of delirium (8–10). However, there have been no studies investigating the association between systemic inflammatory markers and delirium diagnosis in pediatric patients.

Our objective in this study was to investigate the relationship between systemic inflammatory markers and the development of delirium in critically ill children. We hypothesized that inflammation, as measured by C-reactive protein (CRP) and procalcitonin levels, would be associated with pediatric delirium.

Materials and Methods

The Weill Cornell Medical College Institutional Review Board approved this retrospective cohort study. This study took place in an urban, academic, tertiary PICU. Included patients were aged 0–21 years old and admitted to the PICU between January 1, 2015 and December 31, 2017. To be included in the study, the patient had to be screened for delirium and have had a procalcitonin or CRP level drawn during the first 14 days of their PICU stay.

A list of all PICU patients with procalcitonin or CRP drawn within our desired date range was provided by the New York-Presbyterian analytics department. Demographic and clinical information for each patient was extracted from the electronic medical record. Information of interest included age, sex, admission diagnosis, respiratory support, severity of illness, length of PICU stay, and mortality. Severity of illness was determined by the Pediatric Index of Mortality-3 (PIM-3) score (11). Data were entered into REDCap (Research Electronic

Data Capture), a secure, web-based application providing an intuitive interface for validated data entry (12).

Each child was assigned a cognitive status for each study day: delirium, coma, or delirium-free/coma-free (i.e. normal cognitive status). Delirium status was determined by the Cornell Assessment of Pediatric Delirium (CAPD), a validated observational tool consisting of eight questions that adequately differentiate between pain, agitation, residual sedation and delirium (13). A score of nine or greater on the CAPD is consistent with a diagnosis of delirium. Delirium was divided into its three categories: hypoactive, hyperactive, or mixed delirium, based on motor symptoms. Coma status was determined by the Richmond Agitation Sedation Scale (RASS) (14). Patients were determined to be comatose if they scored a -4 or -5 on the RASS (i.e. unarousable to verbal stimulation) for the entire study day. Patients who were neither delirious nor comatose on a specific day were determined to be delirium-free/ coma-free (DFCF). If delirium/coma status was not recorded on a particular day, the status was “unknown.”

CRP and procalcitonin levels were sent at the discretion of the treating physician. CRP was reported in mg/dL with a normal value of 0.9, and procalcitonin was reported in ng/mL with a normal value of <0.08. If a CRP/procalcitonin was sent within the first 48 hours of admission, it was designated as an initial level. Every CRP/procalcitonin which was sent within the first 14 PICU days was included in analyses. Maximum and median CRP/procalcitonin were determined for each subject.

Statistical Analysis

Patient characteristics were described as N (%) or mean, standard deviation, and spread as appropriate. Initial, maximum, and median CRP/procalcitonin levels were captured for each patient, and reported as median and interquartile range. At the daily level, inflammatory markers (CRP/procalcitonin) were compared by daily cognitive status (delirium/coma/DFCF) using Kruskal-Wallis/Wilcoxon rank-sum tests. At the patient level, duration of delirium and DFCF days were categorized based on tertiles; CRP/procalcitonin markers (initial, maximum, and median) were compared between these groupings using Kruskal-Wallis tests. Initial, maximum, and median inflammatory markers were also divided into tertiles (low/medium/high) and compared with delirium incidence, delirium duration, and DFCF days by Chi-square/Fisher's Exact tests or Kruskal-Wallis tests. All analyses were two-sided with statistical significance evaluated at the 0.05 alpha level. Analyses were performed in R version 3.5.1 (Vienna, Austria).

Results

A total of 734 patients were included in this study. 664 patients (90.4%) had a CRP drawn and 587 (80%) had a procalcitonin drawn. 522 patients (71.1%) had both CRP and procalcitonin sent. 58% (n=426) of patients were male, and many were under two years of age (41.4%, n=304). The most common admitting diagnosis was respiratory insufficiency (33.5%, n=246). The median PICU length of stay was 6 days [IQR 3.00–11.0] and the median hospital length of stay was 9 days [IQR 5.00–17.0]. The mean probability of

mortality as generated by the PIM-3 score was 3.2% [$\pm$ 7.1%]. The in-hospital mortality rate in this cohort was 1.6% (n=12) (Table 1).

37.3% (n=274) of the patients in this cohort were delirious at some point during the first 14 days of PICU stay. Of the total 5165 patient days on which daily cognitive status was recorded, 1110 patient days (21.5%) were categorized as days with delirium. 484 days (9.4%) were classified as days with coma. 3217 days (62.3%) were categorized as DFCF. On 354 days (6.9%), there was no cognitive status recorded.

Amongst the 274 children with delirium in this cohort, median duration of delirium was three days [IQR 1–6]. When categorized by subtype, hypoactive was the most common subtype (71%), followed by mixed delirium (23%). Hyperactive was the least common subtype, with only 6%.

Patients with higher severity of illness on admission (as quantified by the probability of mortality (POM) generated by the PIM-3 score) were more likely to develop delirium (median POM 1% (IQR 1–2%) in children who developed delirium vs 2% (IQR 1–4%) in children who did not develop delirium, $p < 0.001$). Mortality rate in the children who experienced delirium was 4.4% as compared to a mortality rate of 0% in children who were DFCF throughout their hospital stay ($p = 0.005$).

Within the 664 patients who had CRP drawn, there was a total of 1266 CRP samples sent within the first 14 days of admission to the PICU (median 1 sample/subject; IQR 1–2). The median initial CRP level was 4.00 mg/dL [IQR 0.70–12.4]. Maximum CRP level was 5.39 mg/dL [median; IQR 1.20–14.8]. In bivariate analysis, median CRP levels were higher on DFCF days when compared to a day with delirium and/or coma (Figure 1). The median CRP level on a day with delirium was 5.6 mg/dL [IQR 1.28–13.0], on a day with coma was 4.66 mg/dL [IQR 1.75–11.5], and on a DFCF day was 6.40 mg/dL [IQR 1.60–15.6] ($p = 0.117$) (Table 2).

Within the 587 patients who had procalcitonin drawn, there was a total of 1063 procalcitonin samples sent within the first 14 days of admission to the PICU (median 1 sample/subject; IQR 1–2). The median initial procalcitonin was 0.79 ng/mL [IQR 0.20–6.81]. Maximum procalcitonin was 0.81 ng/mL [median; IQR 0.18–6.17]. In bivariate analysis, median procalcitonin levels were higher on coma days, but lowest on delirium days (Figure 1). The median procalcitonin level on a day with delirium was 0.50 ng/mL [IQR 0.14–2.94], on a day with coma was 1.62 ng/mL [IQR 0.21–8.43], and on a DFCF day was 1.13 ng/mL [IQR 0.30–5.65] ($p < 0.001$) (Table 2).

In exploratory analyses, we assessed the relationship between CRP/procalcitonin and DFCF days, as well as delirium duration. This too did not achieve significance. Relationships were analyzed in several ways: initial CRP/procalcitonin and delirium incidence (defined as delirium at any point during the first 14 days of the PICU stay); maximum CRP/procalcitonin and delirium incidence; initial CRP/procalcitonin and number of DFCF days; maximum CRP/procalcitonin and number of DFCF days. We also divided CRP and procalcitonin into tertiles and assessed relationship with delirium incidence, delirium duration, and number of DFCF days. Finally, we assessed the association between CRP/

procalcitonin and specific delirium subtype (hyperactive v. hypoactive v. mixed). In every analysis, no significant relationship was found between level of inflammatory marker and delirium.

Discussion

In this retrospective cohort study, we assessed the relationship between markers of systemic inflammation and development of delirium. There was no relationship found between either CRP or procalcitonin and development of any delirium subtype during the first two weeks of patients' PICU stay.

In designing this study, we hypothesized that inflammation plays a pathophysiologic role in the development of pediatric delirium. An international point prevalence study showed that critically ill children admitted with a systemic inflammatory disorder had highest delirium rates (42%) when compared with children admitted for other reasons ($p=0.017$) (3). This is consistent with the neuroinflammatory hypothesis of delirium, which postulates that cytokines released in a systemic inflammatory state increase the permeability of the blood brain barrier. This leads to alteration of neurotransmitter function, which results in the acute and fluctuating change in cognition and behavior that is diagnostic of delirium (7,15). As direct markers of neuroinflammation are not readily available, we hypothesized that peripheral markers of inflammation (the widely used CRP and procalcitonin) would reflect neuroinflammation. This was supported by a study in critically ill adults, that demonstrated a relationship between CRP and procalcitonin levels at admission and duration of delirium (8). Another recent study in delirious adults showed an association between CRP level at time of delirium onset, and delirium duration and severity (10). In addition, a meta-analysis of 54 observational studies found that CRP levels were increased in patients who experienced postoperative delirium (9).

However, in contrast to adult studies, no relationship was observed between CRP/procalcitonin and a diagnosis of delirium in our cohort. In fact, in certain analyses, there was a trend suggesting that the inverse may be true (patients with higher inflammatory markers were less likely to be delirious). As a result, we have concluded that it is likely that neither CRP nor procalcitonin are useful markers for delirium in critically ill children.

Alternatively, it is possible that our retrospective study design limited our ability to adequately test this relationship. As opposed to a prospective study in which every patient has a CRP/procalcitonin drawn upon PICU admission, we were restricted to only patients who had a CRP/procalcitonin drawn for clinical reasons. This introduces a selection bias, as it is likely that the patients included in our study were those in whom clinicians already suspected systemic inflammation (and therefore obtained CRP/procalcitonin levels) and these patients were therefore already at heightened risk for delirium. It is notable that the delirium rate in our cohort was 37%, which is significantly higher than delirium rates in our PICU overall (17%), and consistent with delirium rates reported in children with underlying inflammatory processes (42%) (2,3). Another explanation for the lack of relationship between inflammatory marker levels and delirium is that we may be using the wrong markers of inflammation to evaluate the relationship.

Further studies will be necessary to investigate the role of neuroinflammation in the pathophysiology of pediatric delirium. Specific markers of neuroinflammation should be tested, in particular the proteins S-100B and Tau, as these have been linked to delirium in adult studies. For example, an observational study of 22 patients in septic shock found that patients with an S-100B >0.15 ng/dL had increased odds of developing delirium (OR 18.0, 95% CI 1.7–196.3, $p=0.011$) (16). In another study, median levels of the brain protein Tau were higher in patients with delirium when compared to those without (90 [IQR 46–224] vs. 31 [IQR 31–52], $p=0.009$) (17). Such studies have not been conducted in the pediatric population.

The most important limitation of this study is its retrospective design, which selected for patients who were already suspected to have systemic inflammation, and did not include the rest of the PICU population. It is possible that a future prospective study, with initial CRP/procalcitonin drawn in all PICU patients, may show that markers of systemic inflammation can predict development of delirium. In addition, the single-center nature of this study is a limitation, as results may not be readily generalizable. However, this study has several strengths including a large sample size ($n=734$) which should have provided enough power to show a statistically significant relationship between CRP/procalcitonin and delirium if one truly existed. Furthermore, the data set was very complete, with daily cognitive status available for >93% of our 5165 patient days. Despite the null results, it is important to disseminate these findings to aid the research community in designing future studies to investigate the potentially significant role of neuroinflammation in the pathogenesis of pediatric delirium (18).

Conclusion

In this retrospective cohort of pediatric critically ill patients, neither CRP nor procalcitonin was associated with delirium. It will be necessary to conduct preclinical, translational, and prospective clinical studies to further investigate the relationship between inflammation and pediatric delirium.

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Figure 1. Box-and-whisker plots showing levels of C-reactive protein [CRP] (A) and procalcitonin (B) on days with delirium, coma, and normal cognitive status (delirium-free/coma-free [DFCF]).

Table 1:Patient Demographic and Clinical Information ($n=734$)

Characteristic	<i>n</i> (%)
Age Category	
0–2 years	304 (41%)
>2–5 years	113 (15.4%)
>5–13 years	166 (22.6%)
>13 years	151 (20.6%)
Sex	
Male	426 (58%)
Female	308 (42%)
Admitting Diagnosis Category	
Respiratory Insufficiency/Failure	246 (33.5%)
Infectious/ Inflammatory Disease	188 (25.6%)
Neurologic Disorder	122 (16.6%)
Cardiac Disease	80 (10.9%)
Renal/Metabolic Disorder	56 (7.6%)
Hematologic/Oncologic Disorder	42 (5.7%)
Mechanical Ventilation	
Yes	274 (37.3%)
No	460 (62.7%)
Probability of Mortality[*]	3.2% [$\pm$ 7.1%]
In-Hospital Mortality	
Yes	12 (1.6%)
No	722 (98.4%)
Ever Delirious	
Yes	274 (37.3%)
No	460 (62.7%)

^{*} As determined by the Pediatric Index of Mortality-3 Score

Table 2:

Inflammatory Markers in Study Cohort

Characteristic	CRP (n=664)		Procalcitonin (n=587)	
Number of levels sent per patient	1 [IQR 1–2]		1 [IQR 1–2]	
Initial level *	4.00 [IQR 0.70–12.4] (n=490)		0.79 [IQR 0.20–6.81] (n=417)	
Max level **	5.39 [IQR 1.20–14.8]		0.81 [IQR 0.18–6.17]	
Level on Day with Delirium	5.60 [IQR 1.28–13.0]	p = 0.117	0.50 [IQR 0.14–2.94]	p < 0.001
Level on Day with Coma	4.66 [IQR 1.75–11.5]		1.62 [IQR 0.21–8.43]	
Level on day without delirium or coma	6.40 [IQR 1.60–15.6]		1.13 [IQR 0.30–5.65]	

Results reported as median

* CRP or procalcitonin obtained within the first 48 hours of PICU stay

** Maximum level obtained any time within first 14 days of PICU stay