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Insulin-Like Growth Factor-1 and Delirium in Critically Ill Mechanically Ventilated Patients: A Preliminary Investigation

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Abstract

Background—Delirium is frequent in the ICU but its pathophysiology is still unclear. Low levels of insulin-like growth factor 1 (IGF-1), a hormone with neuroprotective properties, has been associated with delirium in some non-ICU studies, but this relationship has not been examined in the ICU. We sought to test the hypotheses that low IGF-1 concentrations are associated with delirium during critical illness.

Methods—Mechanically ventilated medical ICU patients were prospectively enrolled and blood was collected after enrollment for measurement of IGF-1 using radioimmunoassay. Delirium and coma were identified daily using the Confusion Assessment Method for the ICU and the Richmond Agitation-Sedation Scale, respectively. The association between IGF-1 and delirium was evaluated with logistic regression. Also, the association between IGF-1 and duration of normal mental status, measured as days alive without delirium or coma, was assessed using multiple linear regression.

Results—Among 110 patients, median age was 65 years (IQR, 52–75) and APACHE II was 27 (IQR, 22–32). IGF-1 levels were not a risk factor for delirium on the day after IGF-1

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measurement ($p=0.97$), at which time 65% of the assessable patients were delirious. No significant association was found between IGF-1 levels and duration of normal mental status ($p=0.23$).

Conclusions—This pilot study, the first to investigate IGF-1 and delirium in critically ill patients, found no association between IGF-1 and delirium. Future studies including serial measurements of IGF-1 and IGF-1 binding proteins are needed to determine whether this hormone has a role in delirium during critical illness.

Keywords

Insulin-Like Growth Factor-1; delirium; acute brain dysfunction; coma; critical illness; intensive care unit; elderly

Introduction

Older patients, who account for more than half of intensive care unit (ICU) admissions and accrue 60% of all ICU days in the United States (Angus *et al.*, 2000), frequently experience delirium during critical illness. This form of acute brain dysfunction, in fact, affects up to 80% of mechanically ventilated ICU patients (Girard *et al.*, 2008b) and is associated with numerous adverse outcomes in this vulnerable population, including prolonged hospitalization (Girard *et al.*, 2008b), increased costs (Girard *et al.*, 2008b), higher short- and long-term mortality (Girard *et al.*, 2008b; Pisani *et al.*, 2009), and persistent brain dysfunction in the form of long-term cognitive impairment (Girard *et al.*, 2010).

A variety of mechanisms have been proposed to explain the pathophysiology of delirium; these include inflammation, abnormalities in neurotransmission, and direct effects of medications, e.g., sedatives and analgesics, etc (Gunther *et al.*, 2008; Inouye and Ferrucci, 2006). In particular, several studies have examined the association of delirium with markers of inflammation, such as inflammatory and anti-inflammatory cytokines (Gunther *et al.*, 2008; Inouye and Ferrucci, 2006). Insulin-like growth factor 1 (IGF-1) has also been considered in the pathogenesis of delirium since this hormone, referred to by some investigators as a “neuroprotective cytokine,” inhibits cytotoxic cytokines (e.g., IL-6, IL-8, IL-1), an effect that may be especially important during an acute critical illness.

Low IGF-1 concentrations, in fact, have been associated with the development of delirium in acutely ill, older patients (Wilson *et al.*, 2005; Adamis *et al.*, 2007; Adamis *et al.*, 2009), suggesting that patients with low IGF-1 may lack innate neuroprotection against chemical and physical insults, making them more susceptible to the development of delirium. Studies examining IGF-1 and delirium, however, have not uniformly found such an association. Lemstra *et al.* (Lemstra *et al.*, 2008), for example, found preoperative IGF-1 concentrations did not predict postoperative delirium in older hip surgery patients.

Based on studies conducted outside the ICU, we suspected that IGF-1 may be associated with delirium in ICU patients; no data, however, are currently available regarding the relationship between IGF-1 levels and delirium during critical illness. Therefore, we prospectively tested the hypothesis that low IGF-1 concentrations early during critical illness would be associated with delirium in mechanically ventilated medical ICU patients.

Methods

Study Design and Population

This was a prospective cohort study nested within the Awakening and Breathing Controlled (ABC) randomized trial (Girard *et al.*, 2008a), which evaluated a sedation and ventilator

weaning protocol for mechanically ventilated medical ICU patients. Participants who were enrolled in the ABC trial at Saint Thomas Hospital (Nashville, TN) after May 2004 and had blood available for measurement of IGF-1 were included in the current cohort study. Inclusion criteria were adult medical ICU patients who were mechanically ventilated >12 hours. Patients were excluded if they were: 1) admitted after cardiopulmonary arrest, 2) ventilated >2 weeks prior to screening, 3) enrolled in another trial, 4) moribund, 5) profoundly neurologically impaired at baseline (i.e. large stroke or severe dementia), or 6) lacking surrogate consent or physician agreement (Girard *et al.*, 2008a).

Informed consent was obtained at enrollment from an available surrogate, and the participants themselves provided consent once capable. The institutional review boards at Saint Thomas Hospital and Vanderbilt University approved the study protocol.

Demographics and Baseline Characteristics

At enrollment, demographics and baseline characteristics were collected from the medical record and using validated surrogate questionnaires. Activities of daily living (ADLs) were assessed using the Katz ADL; scores 0–1 were considered indicative of ADL “independence,” 2–4 indicated “partial disability,” and 5–6 indicated “total dependence.” (Katz *et al.*, 1963) Impairment in instrumental activities of daily living (IADLs) were identified using the Functional Activities Questionnaire (FAQ) with scores >10 indicating impaired functioning. (Pfeffer *et al.*, 1982)

To identify preexisting cognitive impairment, we used the Short Informant Questionnaire of Cognitive Decline in the Elderly (Short IQCODE) (Jorm, 1994). Patients with an IQCODE score >4 were considered to have preexisting cognitive impairment.

Exposure, covariates and outcomes

Blood for measurement of serum IGF-1 concentration, the primary exposure variable, was collected within 48 hours of study enrollment and processed within 4 hours of collection. Specifically, specimens were centrifuged, and serum was removed and stored at –80°C Celsius (C). A radioimmunoassay kit (Alpo Diagnostic, NH), modified to optimize sensitivity, was used for batched, quantitative measurement of serum IGF-1 concentrations, as previously reported (Landi *et al.*, 2007). IGF-1 values of 292, 282, 287, 207 and 184 ng/ml are considered in the 95th percentile for IGF-1 levels in adults age 50–60, 60–70, 70–80, and >80, respectively (Blum and Breier, 1994).

Three covariates were selected *a priori*: age, severity of illness and severe sepsis. Severity of illness was determined using Acute Physiology and Chronic Health Evaluation II (APACHE II) (Knaus *et al.*, 1985). Severe sepsis at ICU admission was identified using treating physicians' admission diagnoses and confirmed to meet internationally standardized criteria: presence of two of the four Systemic Inflammatory Response Syndrome Criteria (i.e., body temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO₂<32 mmHg, WBC>12,000/mm³, <4000/mm³, or >10% immature- band forms) with suspected or proven infection and organ dysfunction (Levy *et al.*, 2003).

Patients were assessed twice daily for delirium, the primary outcome, by trained research personnel using the Confusion Assessment Method for the ICU (CAM-ICU) (Ely *et al.*, 2001). Level of consciousness was assessed using the Richmond Agitation-Sedation Scale (RASS) (Sessler *et al.*, 2002). Both assessments were continued until ICU discharge, death, or study conclusion. Patients were categorized as comatose if they were unresponsive to verbal and physical stimuli (RASS –5) or responsive only to physical stimuli (RASS –4); they were considered delirious if they were not comatose (i.e., RASS –3 to +4) and had a positive CAM-ICU assessment.

To avoid potential confounding by death and coma in our analysis of duration of normal mental status, a secondary outcome, we calculated the number of days in the 14 days after enrollment during which patients were alive without delirium or coma, as previously described. (Pandharipande *et al.*, 2007) Multiple imputation based on the previous and next day's observed mental status was used in the case of a missing mental status assessment. Though none of delirium assessments used in the primary analysis were missing, multiple imputation based on the previous and next day's observed mental status was used in the calculation of delirium/coma-free days because mental status assessments were missing for 31 (2%) of the 1540 patient-days included in this secondary analysis.

Statistical Analysis

Baseline demographics and clinical characteristics are presented using medians and interquartile ranges for continuous variables and proportions for categorical variables. In our primary analysis, we examined the association between IGF-1 concentrations and the probability of delirium the day following IGF-1 measurement using logistic regression. Only patients who could be assessed for delirium the day after IGF-1 measurement were included in this analysis; comatose patients, as well those who died or were discharged shortly after blood was collected (and prior to outcome assessment), were excluded. In a secondary analysis, we examined the association between IGF-1 concentrations and duration of normal mental status (i.e., days alive without delirium or coma) using a multiple linear regression.

To adjust for potential confounders, age, severe sepsis and the acute physiology score of APACHE II were included in all regression models as covariates. IGF-1 was log transformed to improve model fit. Nonlinearity of all associations between IGF-1 and outcomes was assessed using restricted cubic splines; we planned *a priori* to retain the nonlinear term in each regression model unless the association was clearly linear (p for nonlinear term > 0.20).

Because IGF-1 concentrations have been found to be low in patients with sepsis (Ashare *et al.*, 2008), and since sepsis is a frequent ICU admission diagnosis, all regression models were constructed with and without adjustment for sepsis in order to gain insight into a potential causal pathway. All statistical analyses were performed using R version 2.7 (www.r-project.org).

Results

From June 2004 to March 2006, blood was collected for measurement of IGF-1 from 110 patients. Baseline demographics and clinical characteristics of these patients are described in Table 1. The median [Interquartile Range] time between ICU admission and study enrollment was 1.9 [1.2–3.3] days. Acute brain dysfunction was common, with 78% delirious and 74% of patients comatose at some point during the 14-day study period. Thirty (25%) patients died during the study period. On the day following IGF-1 measurement, 2 patients had died and 46 patients were comatose, precluding delirium assessment at that time. Of the 62 patients who were alive and not comatose, and therefore assessed with the CAM-ICU, 40 (64%) were delirious.

IGF-1 concentrations were not associated with delirium on the day after IGF-1 measurement, regardless of adjustment for sepsis ($p=0.97$ and 0.93 , respectively) (Table 2, Figure). IGF-1 concentrations were also not significantly associated with duration of normal mental status (Table 2) either before or after adjustment for sepsis ($p=0.27$ and 0.23 , respectively).

Discussion

In this pilot investigation, the first to our knowledge to evaluate the relationship between IGF-1 and delirium in the ICU, IGF-1 concentrations early during critical illness were not associated with delirium or duration of normal mental status.

IGF-1 is a hormone produced primarily in the liver when stimulated by growth hormone. Although many of growth hormone's effects on cell growth are mediated directly through the growth hormone receptor, the hormone also affects body growth and metabolism through stimulation of IGF-1 production. Reinhardt and Bondy (Reinhardt and Bondy, 1994) demonstrated that liver-derived circulating IGF-1 crosses the blood-brain barrier, after which it can bind IGF-1 receptors believed to be expressed throughout the brain, especially in the superficial and deep cortical layers, olfactory bulb, amygdala, thalamic nuclei and hippocampus. In animal studies, IGF-1 has been shown to regulate stem cell differentiation into neurons (Brooker *et al.*, 2000) and induce neurogenesis of the hippocampus (Aberg *et al.*, 2000). IGF-1 and its binding proteins have therefore been examined in a variety of brain diseases (e.g., Alzheimer's disease, stroke, and multiple sclerosis) (Trejo *et al.*, 2004).

Few studies to date, all conducted outside the ICU and including from 67 to 164 patients, have analyzed IGF-1 as a risk factor for or predictor of delirium (Adamis *et al.*, 2009; Wilson *et al.*, 2005; Adamis *et al.*, 2007). The lack of an association between IGF-1 and delirium in our investigation is similar to the findings of Lemstra *et al.* (Lemstra *et al.*, 2008), who found that preoperative IGF-1 concentrations did not predict the occurrence of postoperative delirium in their study of 68 older hip surgery patients. Other studies, alternatively, have found low IGF-1 to be associated with incident and prevalent delirium in older patients admitted to medical wards (Adamis *et al.*, 2009; Wilson *et al.*, 2005; Adamis *et al.*, 2007). In contrast to these investigations, we studied a population consisting of critically ill ICU patients. For example, Wilson *et al.* (Wilson *et al.*, 2005) excluded severely ill patients who could not provide consent, a characteristic common during the early days of an ICU stay; Adamis *et al.* excluded intubated patients from their studies (Adamis *et al.*, 2007; Adamis *et al.*, 2009). The often multifactorial nature of delirium in the ICU may obscure the role of IGF-1 previously noted, especially given the higher number of predisposing and precipitating risk factors affecting severely ill patients. In light of earlier results, future larger studies including serial measurements of IGF-1 in the ICU are needed before a relationship between this neuroprotective hormone and delirium during critical illness can be ruled out.

Our study has important strengths including prospective, daily neurologic assessments by trained research personnel using a validated delirium assessment tool (i.e., the CAM-ICU) and a validated sedation scale (i.e., the RASS) as well as a study population at high risk for delirium, i.e., critically ill patients, half of whom were older patients.

This study, however, has limitations. We did not measure, for example, other related biomarkers including growth hormone and IGF-binding proteins. High levels of growth hormone may lead to insulin resistance, which has been thought to influence clinical outcomes through alterations of IGF-1 and insulin-like growth factor 1 binding proteins (IGFBP) in critically ill patients (Basi *et al.*, 2005). Timmins *et al.* (Timmins *et al.*, 1996) reported low levels of IGFBP-3 in ICU patients. IGFBP-3 is the main IGF-1 binding protein; it carries 90%–95% of the circulating IGF-1 in a ternary complex with acid-labile subunit (Baxter *et al.*, 1989). Low levels of IGFBP-3 are considered to increase the bioavailability of IGF-1 to counteract the effect of insulin resistance and subsequently a hyperglycemic status. IGF-1 actually increases insulin sensitivity, through enhanced peripheral glucose reuptake and decreased hepatic glucose production (Boulware *et al.*, 1994). However, high levels of

IGF-1 are reported to be responsible for symptomatic hypoglycemia (Zenobi *et al.*, 1992). The glycemic perturbation might also be related to neurological outcomes. In the current investigation, no data were collected on the glycemic changes during the course of the critical illness.

Studies show that IGF-1 and IGFBP-3 concentrations are low during the course of a critical illness, findings that can persist for 7 days or more (Baxter *et al.*, 1998; Timmins *et al.*, 1996). Alternatively, increases in IGF-1 levels during the course of illness have been noted and reported to be a sign of recovery from the critical illness (Baxter *et al.*, 1998; Timmins *et al.*, 1996); changes in IGF-1 levels over time, therefore, might have a relationship with recovery from delirium. Since we only measured IGF-1 at baseline, we were unable to examine potential associations between changes over time in IGF-1 concentrations and delirium. Because the median ICU length of stay was about a week in our study, we suspect that IGF-1 concentrations were low during the entire course of the ICU stay. Nevertheless, future studies should include serial measurements of IGF-1 and IGFBP-3 to better clarify the role of the growth hormone-IGF-1 axis in the neurological effects of critical illness. Changes in IGF-1 and IGFBP-3 over time might be important determinants of neurological outcomes even if baseline IGF-1 concentrations are not.

Finally, because of the relatively small size of our pilot study, we were limited in the number of covariates we could adjust for in the regression models; the inclusion of additional covariates, such as preexisting functional and cognitive impairment—both potential risk factors for delirium—would increase the risk of overfitting in the regression models, i.e., increasing the chance of obtaining a significant result due to random error or noise. Future larger studies that adjust for these and other potential confounders as well as include serial measurements of IGF-1 and IGFBP-3 may better clarify the role of the growth hormone-IGF-1 axis in the neurological effects of critical illness.

Conclusions

This pilot study is the first to analyze potential associations between IGF-1 concentrations early in critical illness and delirium in the ICU. No association was found between baseline IGF-1 levels and either delirium or duration of normal mental status in critically ill patients. Future studies, including sequential samples of IGF-1 and its related binding proteins, are needed to further clarify the relationship between the growth hormone-IGF-1 axis and acute neurological outcomes during critical illness.

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Description of authors' roles: Study conception and design – All authors. Acquisition of data – Morandi, Girard. Data analysis – Thompson, Shintani. Interpretation of results – All authors. Drafted manuscript – Morandi. Critically revised the manuscript – All authors. Final approval of manuscript – All authors.

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Figure 1. Insulin-like growth factor 1 (IGF-1) and delirium

IGF-1 concentrations were not associated with risk of delirium on the day after IGF-1 measurement ($p=0.97$), adjusting for age, severity of illness, and severe sepsis at ICU admission.

Table 1

Demographics and clinical characteristics of the study population

Variable ^a	Entire Sample (N= 110)	Patients Included in Primary Analysis ^b (N=62)
Age, y	65 (52 to 74)	66 (53 to 76)
Men, No. (%)	57 (52%)	35 (57%)
IQCODE at baseline	3 (3.0 to 3.19)	3 (3.0 to 3.12)
Cognitive impairment at baseline, No. (%) ^c	9 (8%)	5 (8%)
ADL categories at baseline, No. (%) ^d		
Fully independent	95 (85%)	44 (85%)
Partially dependent	10 (9%)	6 (12%)
Totally dependent	5 (5%)	2 (4%)
IADL impairment at baseline, No (%) ^e	21 (20%)	11 (22%)
APACHE II at enrollment	27 (22 to 32)	25 (22 to 31)
SOFA at enrollment	9 (7 to 12)	7 (9 to 12)
ICU length of stay	7.5 (4.6 to 13.3)	7.6 (4.6 to 13.4)
Hospital length of stay	9.8 (7.1 to 16.3)	9.8 (7.1 to 16.4)
Admission diagnoses, No. (%)		
Sepsis/acute respiratory distress syndrome	48 (44%)	24 (38%)
Myocardial infarction/congestive heart failure	20 (18%)	12 (20%)
Altered mental status	15 (14%)	11 (17%)
Chronic obstructive pulmonary disease/asthma	9 (8%)	4 (6%)
Other ^f	18 (16%)	11 (18%)
IGF-1 at baseline, (ng/ml)	131 (97 to 194)	125 (93 to 179)
Duration of brain dysfunction, days		
Delirium	2 (1 to 4)	2 (1 to 4)
Coma	0.5 (0 to 2)	0 (1 to 2)

Abbreviations: IQCODE, Short Informant Questionnaire of Cognitive Decline in the Elderly; ADL, activities of daily living; IADL, Instrumental Activities of Daily Living; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive care unit; IGF-1, insulin-like growth factor 1.

^aMedian (interquartile range) unless otherwise noted.

^bClinical and demographic characteristics of patients alive and not comatose on the day after the IGF-1 sample were drawn. These patients were included in the primary analysis to test the association between IGF-1 concentrations and the probability of delirium the day following IGF-1 measurement.

^cPatients with an IQCODE score = 4 were considered to have preexisting cognitive impairment, presumably of mild to moderate severity, because we excluded patients from study enrollment with dementia that prevented them from living independently.

^dADL were defined according the Katz scale: 0–1 were “independent,” 2–4 were “partial disability,” and 5–6 were “total dependence. (Katz *et al.*, 1963)

^eIADL were defined with the Functional Assessment (FAQ) with score = 10 indicating impaired functioning. (Pfeffer *et al.*, 1982)

^fIncluding gastrointestinal bleeding, metabolic disarray, haemoptysis, pulmonary embolism, and status epilepticus.

Table 2Insulin-like growth factor-1 and neurologic outcomes^a

Outcome	Odds Ratio	95% CI	P Value
Delirium risk	1.0	0.6 to 1.8	0.97
Duration of acute brain dysfunction	Nonlinear ^b		0.22

^aAll associations were adjusted for age, severity of illness, and severe sepsis at ICU admission.

^bThe relationship between Insulin-like-growth factor-1 and delirium was nonlinear; thus a single odds ratio cannot estimate this association.