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The Stress Response to Surgery and Postoperative Delirium: Evidence of Hypothalamic—Pituitary—Adrenal Axis Hyperresponsiveness and Decreased Suppression of the GH/IGF-1 Axis

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Abstract

Introduction: The aim of this study is to determine whether postoperative delirium is associated with dysregulation of hypothalamic—pituitary—adrenal and growth hormone/insulin-like growth factor 1 (GH/IGF-1) responses following acute systemic inflammation. **Methods:** Plasma levels of cortisol, IGF-1, C-reactive protein, interleukin (IL)-6, IL-8, and IL-10 were measured before and after surgery in 101 patients $\geq$60 years without dementia undergoing elective hip arthroplasty. Participants were assessed with confusion assessment method and *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; *DSM-IV-TR*) postoperatively and 37 patients fulfilled the *DSM-IV-TR* criteria for delirium. **Results:** Preoperative plasma cortisol levels were similar in delirium and nondelirium groups (405.37 $\pm$ 189.04 vs 461.83 $\pm$ 219.39; $P = .22$). Participants with delirium had higher postoperative cortisol levels (821.67 $\pm$ 367.17 vs 599.58 $\pm$ 214.94; $P = .002$) with enhanced postoperative elevation in relation to baseline (1.9- vs 1.5-fold; $P = .004$). The plasma levels of IGF1 did not differ in delirium and nondelirium groups before (18.12 $\pm$ 7.58 vs 16.8 $\pm$ 7.86; $P = .477$) and following surgery (13.39 $\pm$ 5.94 vs 11.12 $\pm$ 6.2; $P = .639$), but the levels increased in relation to baseline more frequently in patients who developed delirium (24.3% vs 7.8%; $P = .034$). The magnitude of postoperative cortisol elevation correlated with ΔIL-6 ($P = .485$; $P = .002$), ΔIL-8 ($P = .429$; $P = .008$), and ΔIL-10 ($P = .544$; $P < .001$) only in patients with delirium. **Conclusions:** Hypothalamic—pituitary—adrenal axis hyperresponsiveness and a less frequent suppression of the GH/IGF-1 axis in response to acute stress are possibly involved in delirium pathophysiology.

Keywords

delirium, inflammation, cortisol, insulin-like growth factor 1, interleukins, C-reactive protein

Introduction

Delirium is a clinical syndrome with a rapid-onset of cognitive, emotional, and behavioral symptoms that all emerge in the context of a general medical condition and/or substance use considered to be etiologically related to the symptoms.[1] This syndrome, which is commonly diagnosed in inpatient medical and surgical settings, is a result of simultaneous interactions between preexisting predisposing factors (eg, advanced age and dementia) and acute precipitants (eg, surgical trauma, infection, and medications).[2] Irrespective of the underlying causes, a common feature of delirium pathophysiology is the acute and transient impairment in the homeostatic balance of the central nervous system (CNS) comparable to the concepts of renal or hepatic insufficiency.[3] In healthy individuals, the conjoined action of the immune and endocrine systems is crucial to recover stability and regain homeostasis.[4,5] Understanding the neuroadaptive characteristics of patients prone to develop acute confusion when exposed to acute stress factors, therefore, is of outmost importance.

The CNS responds to a plethora of circulating inflammatory mediators through production of an acute neuroinflammatory response (mediated by microglial cells and astrocytes) and activation of the major neuroendocrine pathways including the hypothalamic—pituitary—adrenal (HPA) axis. Inadequate activation of

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this innate response, which coordinates a central response to infection and/or tissue damage, is associated with adverse postoperative outcomes (see Kashiwabara et al[6]) and implicated in delirium pathophysiology.

Several aspects of the innate immunity and HPA axis activity are affected with increasing age. The aging process is associated with a sustained 2- to 4-fold increase in the baseline levels of circulating inflammatory mediators.[7] Although some older people maintain the HPA function similar to younger individuals,[8,9] others show increased baseline cortisol levels.[10-12] The neuroinflammatory hypothesis of delirium considers that exaggerated activation of the innate immune system in the brain results in functional changes in neurons and their synapses as well as in cognitive and behavioral features.[13-15] Moreover, changes in the HPA axis activity during aging are not only associated with several age-related pathologies, including dementia,[16,17] but also implicated in delirium.[15] Cross-sectional studies have reported higher cortisol levels in plasma[18,19] and cerebrospinal fluid (CSF)[19] during a delirium episode. Longitudinal studies have similarly found increased plasma cortisol responses to surgical stress in patients with delirium with preoperative HPA axis dysfunction.[20-22]

The proinflammatory cytokine actions in the body are, at least in part, mediated by indirect changes in growth factor expression and activity of growth promoting hormones such as growth hormone/insulin growth factor 1 (GH/IGF-1).[5] The IGF-1 is implicated in a vast number of physiological functions in tissues related to growth, development, and metabolism, including nerve growth and differentiation, as well as neurotransmitter synthesis and release. Acute inflammation induces a state of "GH resistance," as a part of the body's global regulatory mechanism to restrict growth and energy storage, in which the plasma IGF-1 drops despite an increase in GH.[23] Reciprocally, IGF-1 directly counteracts the activity of proinflammatory cytokines produced in the brain attenuating the neuroinflammatory response and the associated sickness behavior induced by lipopolysaccharide.[24] Yet, only a few studies reported an association between lower IGF-1 plasma levels and prevalent[25-27] or incident delirium,[27] while others failed to find any association.[28,29] In previous studies, IGF-1 measurements were made at a single time point rather than in serial assessments, whereas longitudinal studies designed to accurately capture the relation between the response of the GH/IGF-1 axis and delirium in the context of an acute inflammation are still lacking.

The HPA axis, which has a key role in the regulation of the stress response, is an important research target to understand the acute homeostatic failure associated with delirium. Similarly, the relationship between GH/IGF-1 and delirium is important since this neuroendocrine axis has reciprocal interactions with the innate immune system and regulates diverse physiological processes within the CNS. However, the interactions between the immune and neuroendocrine systems following an acute medical or surgical condition and their effects on cognitive function remain obscure. The current study aims to determine the response of plasma cortisol and IGF-1 following surgical trauma, and their relationship with the innate immune response and postoperative delirium.

Materials and Methods

Participants

Consecutive patients aged 60 and older undergoing elective total hip arthroplasty in the Orthopaedics Department of Coimbra University Hospitals from October 2008 to June 2009, with no dementia or delirium (according to *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition, Text Revision; *DSM-IV-TR*] criteria), were included in this cohort study. A written informed consent was obtained from each patient.

Medical—Surgical Procedures and PeriOperative Factors

Prior to surgery, nonsteroid anti-inflammatory and antiplatelet drugs were discontinued for at least 1 week. General anesthesia was induced with propofol and, following the administration of a muscular relaxant, patients were intubated and mechanically ventilated. Alternatively, regional anesthesia (administration of analgesic medication, eg, levobupivacaine, into the subarachnoid space through a catheter) was used. All patients were monitored during surgery with fluid losses being replaced by intravenous crystalloid solution and, if necessary, transfusion of red blood cells or whole blood. A lateral surgical approach with trochanteric osteotomy was used for the arthroplasty.

Preoperative Assessment

All patients recruited in the study had a baseline evaluation that included a medical history (highlighting the presence of either chronic or acute illness, smoking habits, alcohol consumption, and previous psychiatric or neurologic diseases) and a pharmacological history (medication list based on patients' chronic medications and as-needed drugs received on the day before surgery). Anticholinergic potency of each medication was rated using the anticholinergic drug scale.[30] All patients were assessed with Charlson Comorbidity Index,[31] Barthel Index,[32] Mini-Mental State Examination (MMSE),[33] and Geriatric Depression Scale (15 items).[34] Data obtained from routine preoperative assessment included whole blood count and biochemistry.[35,36]

Postoperative Assessment

Each patient was assessed for delirium with the confusion assessment method[37] (CAM; performed by a trained psychiatrist during a brief interview with the participant that also included the MMSE) on 3 occasions: the first assessment occurred in the evening of the surgery day and was repeated at second and third postoperative days. Positive cases of delirium (according to CAM criteria) were confirmed with *DSM-IV-TR* criteria.[1] The postoperative laboratorial assessment consisted of the whole blood count.

Measurements of Serum Levels of Cortisol, Insulin Growth Factor 1, and Inflammatory Mediators

Venous blood samples were drawn from each patient in the morning of the day before surgery and in the morning of the first postoperative day. Plasma was immediately separated by centrifugation and stored at −80°C until analysis. The blood samples were analyzed blinded to the clinical status of the patient. The concentrations of plasma cortisol and IGF-1 were determined by enzyme-linked immunosorbent assay (ELISA) using colorimetric kits purchased from Alpco (Salem, New Hampshire) and Assay Designs (Ann Harbor, Michigan), respectively. The optical densities were measured using a Bio-Tek Spectrophotometer (Plate Reader) Power Wave XS (Winooski, Vermont). The concentrations were calculated from a best fit standard curve generated by the ELISA kit instructions and using the manufacturer suggested protocols. The lower detection limits of the assays were 11.3 nmol/L for cortisol and 4.47 pmol/L for IGF-1. The concentrations of 3 cytokines (interleukin [IL]-8, IL-6, and IL-10) and C-reactive protein (CRP) were determined using the xMAP Bio-Plex Suspension Array System 200 with multiplex assay kits purchased from Bio-Rad (Hercules, CA) and Invitrogen (Carlsbad, CA). Standard curves were constructed for determination of each analyte concentration according to manufacturers' instructions. The detection limits of the assays were CRP = 0.002 pmol/L; IL-6 = 1.1 pg/mL; IL-8 = 0.5 pg/mL; and IL-10 = 0.9 pg/mL. Samples with undetectable cytokine levels were entered at half of the minimum detection level derived from the standard curve.[37]

Statistical Analysis

Data were analyzed using the *Statistical Package of Social Sciences* (PASW Statistics 17, Release Version 17.0.2; SPSS, Inc, 2009, Chicago, Illinois). The significance of the difference between the pre- and postoperative levels of each biomarker was determined with the Student *t* test for paired samples or Wilcoxon test as a nonparametric alternative. Comparison between delirium and nondelirium groups, for both pre- and postoperative values, was performed with Student *t* test for independent samples (normal distributions) or Mann-Whitney *U* test (nonnormal distributions). Association between pre- and postoperative levels of each biomarker was assessed with Spearman correlation coefficient. The relation between post- and preoperative ratios of neuroendocrine markers ($cortisol_{post/pre}$ and $IGF\text{-}1_{post/pre}$) and the difference between the 2 determinations within patients (end point minus baseline levels, Δ) for each inflammatory marker was assessed with Spearman correlation coefficient. A type I (α) error probability of .05 was considered for all inferential analysis.

Results

Sample Characteristics

A total of 116 patients were eligible to enter the study, 2 of which were excluded because they had preoperative delirium. Blood samples were not available for 13 patients due to the problems with venous puncture or clotting of the blood sample. From the final sample of 101 participants, 37 (36.6%) met diagnostic criteria for delirium (assessed with CAM and confirmed with *DSM-IV-TR*) in at least 1 assessment during the study period. Patients who developed postoperative delirium had similar baseline characteristics as those who did not, except for being less likely to have regular alcohol consumption and lower hemoglobin blood levels (Table 1).

Perioperative Factors

A similar proportion of patients with and without postoperative delirium were exposed to general anesthesia. Surgery duration and intraoperative physiological parameters did not differ in both groups. Not surprisingly, patients undergoing blood transfusion presented with lower hemoglobin levels prior to surgery (12.7 vs 13.9 g/L; $t_{99} = 3.948$; $P < .001$). The surgery induced a decrease in hemoglobin levels and elevation in leukocyte count in patients with delirium, showing a lower reduction in hemoglobin and a more pronounced leukocyte elevation (Table 2).

Inflammatory Response

No differences were found between the 2 groups regarding the plasma levels of each mediator either pre- or postoperatively (data not shown). Delirium and nondelirium groups had similar intraindividual differences between post- and preoperative levels (Δ) for CRP (15.35 [15.33] vs 14.62 [13.71]; $P = .632$), IL-6 (113.21 [147.21] vs 76.09 [110.56]; $P = .126$), IL-8 (7.57 [13.31] vs 7.04 [12.58]; $P = .47$), and IL-10 (1.27 [3.8] vs 1.11 [3.1]; $P = .524$). There was a robust association between the inflammatory marker response to surgery, with strong correlations between ΔIL-6, ΔIL-8, and ΔIL-10 in both groups (Table 3).

Cortisol

Before the surgical procedure, the plasma cortisol levels were similar in delirium and nondelirium groups (Table 4). Following surgery, the levels were significantly higher in relation to baseline in both groups of patients with delirium, showing higher levels than nondelirious counterparts (Table 4; Figure 1A). The intraindividual postoperative change in relation to the baseline levels ($cortisol_{post/pre}$) had a median of 1.9-fold in patients with delirium, which was significantly higher than the 1.5-fold elevation observed in patients without delirium (Figure 1C). A positive correlation was observed between preoperative and postoperative plasma cortisol levels in the delirium group ($P = .414$; $P = .011$) but not in the nondelirium group ($P = .141$; $P = .267$). There was no correlation between preoperative hemoglobin levels and the cortisol elevation after surgery (data not shown).

Table 1. Baseline Characteristics of the Sample.

	N (%)			
	Total Sample (n = 101)	Delirium (n = 37)	No Delirium (n = 64)	*P* Value
Gender, male	50 (49.5)	15 (40.54)	35 (54.69)	.216[b]
Age[a]	73.04 ± 6.29 (60-89)	73.65 ± 5.87 (64-89)	72.69 ± 6.53 (60-87)	.462[c]
Educational level				
No years of school	20 (19.8)	8 (21.6)	12 (18·7%)	.848[b]
1-4 years	69 (68.3)	24 (64.9)	45 (70·3%)	
>5 years	12 (9.9)	5 (13.5)	7 (10·9%)	
Smoking				
No smoking	82 (81.2)	30 (81·1)	52 (81·3)	1.000[b]
Past or active smoking	19 (18.8)	7 (18·9)	12 (18·7)	
Alcohol				
No active drinking	46 (45.5)	24 (64.86)	22 (34.37)	**.004**[b]
Active drinking	55 (54.5)	13 (35.13)	42 (65.62)	
Charlson Comorbidity Index[a]	0.54 ± 0.75 (0-4)	0.68 ± 0.91 (0-4)	0.47 ± 0.64 (0-3)	.358[d]
MMSE[a]	26.67 ± 2.79 (19-30)	26.43 ± 2.79 (19-30)	26.80 ± 2.83 (19-30)	.385[d]
Barthel Index[a]	90.99 ± 12.59 (45-100)	88.51 ± 14.33 (50-100)	92.42 ± 11.34 (45-100)	.148[d]
GDS[a]	4.47 ± 3.161 (0-12)	4.62 ± 3.04 (0-12)	4.38 ± 3.25 (0-12)	.554[d]
Number of preoperative drugs[a]	3.37 ± 2.43 (0-9)	3.97 ± 2.79 (0-9)	3.02 ± 2.14 (0-9)	.115[d]
Preoperative ADS[a]	0.68 ± 1.06 (0-5)	0.84 ± 1.32 (0-5)	0.59 ± 0.69 (0-3)	.791[d]
Blood leukocyte count (g/L)	7.23 ± 2.45 (4.1-20.3)	6.74 ± 1.71 (4.1-11.4)	7.52 ± 2.76 (4.3-20.3)	.187[d]
Blood hemoglobin (g/dL)	13.54 ± 1.54 (8.3-17.3)	13.16 ± 1.6 (10.6-17.3)	13.75 ± 1.48 (8.3-16.8)	**.022**[d]

Abbreviations: MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; ADS, Anticholinergic Drug Scale.
[a] Mean ± standard deviation (range).
[b] χ^2 test.
[c] Student *t* test.
[d] Mann-Whitney test.
Bold values correspond to *P* value <.05.

Table 2. Intra and Perioperative Variables.

	N (%)			
Variables	Total Sample (n = 101)	Delirium (n = 37)	No Delirium (n = 64)	*P* Value
General anesthesia	68 (67.33)	29 (78.38)	39 (60.94)	.082[b]
Duration of surgery, minutes[a]	184.75 ± 58.59 (90-330)	202.7 ± 70.15 (90-330)	174.38 ± 48.37 (90-330)	.058[c]
Mean intraoperative heart rate, rpm[a]	69.55 ± 10.87 (52.67-114.5)	70.03 ± 10 (55.83-96.25)	69.27 ± 11.42 (52.67-114.5)	.438[c]
Mean intraoperative systolic arterial pressure, mm Hg[a]	125.61 ± 19.55 (84-182.14)	125.07 ± 19 (90.4-182.14)	125.91 ± 20.01 (84-175.8)	.836[d]
Mean intraoperative diastolic arterial pressure, mm Hg[a]	75.85 ± 11.48 (54.5-106.4)	74.89 ± 9.96 (57.33-95.8)	76.4 ± 12.32 (54.5-106.4)	.526[d]
Intraoperative hypotension	38 (37.6)	16 (43.2)	22 (34.3)	.401[b]
Intraoperative oxygen saturation, %[a]	98.04 ± 1.33 (92.5-100)	98.2 ± 1.14 (94.5-99.33)	97.32 ± 5.02 (92.5-100)	.374[c]
Perioperative analgesia	66 (65.35)	24 (64.86)	42 (65.62)	.553[b]
Perioperative blood transfusion	31 (30.69)	15 (40.54)	16 (25)	.08[b]
ΔBlood leukocyte count, g/L	2.17 ± 3.14 (−11.8-9.8)	3.69 ± 3 (−1.1-9.8)	1.29 ± 2.9 (−11.8-7.9)	**.01**[c]
ΔHemoglobin, g/dL	−2.53 ± 1.5 (−5.3-1.8)	−1.9 ± 1.44 (−4.9-0.56)	−2.9 ± 1.43 (−5.3-1.8)	**<.001**[c]

[a] Mean ± standard deviation (range).
[b] χ^2 test.
[c] Mann-Whitney test.
[d] Student *t* test.
Bold values correspond to *P* value < .05.

Insulin-Like Growth Factor 1 Levels

The plasma levels of IGF-1 did not differ in delirium and non-delirium groups before and following surgery (Table 4). The surgical procedure induced a generalized reduction in the plasma levels of IGF-1 in both the groups (Table 4; Figure 1B), with a strong correlation between pre- and postoperative levels in patients with delirium ($P = .737$; $P < .001$) and in those without delirium ($P = .712$; $P < .001$). Only 13.9% of

Table 3. Correlation Between $Cortisol_{post/pre}$ and $IGF\text{-}1_{post/pre}$ With Intraindividual Difference in Inflammatory Markers (Δ).[a]

		ΔIL-6	ΔIL-8	ΔIL-10	$Cortisol_{post/pre}$	$IGF\text{-}1_{post/pre}$
ΔCRP	Delirium	**.535 (.001)**	**.466 (.004)**	**.347 (.036)**	.048 (.776)	**−.477 (.003)**
	No delirium	**.441 (<.001)**	.225 (.073)	**.271 (.030)**	.190 (.132)	**−.345 (.005)**
ΔIL-6	Delirium		**.665 (<.001)**	**.725 (<.001)**	**.485 (.002)**	−.225 (.180)
	No delirium		**.746 (<.001)**	**.696 (<.001)**	.093 (.466)	**−.253 (.044)**
ΔIL-8	Delirium			**.715 (<.001)**	**.429 (.008)**	−.079 (.640)
	No delirium			**.739 (<.001)**	.005 (.970)	−.222 (.078)
ΔIL-10	Delirium				**.544 (<.001)**	−.078 (.646)
	No delirium				.130 (.306)	−.163 (.198)

Abbreviations: $IGF\text{-}1_{post/pre}$; pre- and postoperative levels of insulin-like growth factor 1; IL, interleukin; CRP, C-reactive protein; Δ, postoperative minus baseline levels.
[a] Spearman coefficient (significance).
Bold values correspond to *P* value < .05.

Table 4. Plasma Levels of Cortisol and IGF-1.

	Preoperative			Postoperative			
	Median (IQR)	Mean ± SD	*P* Value[a]	Median (IQR)	Mean ± SD	*P* Value[a]	*P* Value[b]
Cortisol (nmol/L)							
Total sample (n = 101)	433.93 (283.5)	441.15 ± 209.6		627.94 (361.39)	680.94 ± 298.66		**<.001**
Delirium (n = 37)	381.49 (274.4)	405.37 ± 189.04	.220	783.03 (455.99)	821.67 ± 367.17	**.002**	**<.001**
No delirium (n = 64)	465.63 (291.96)	461.83 ± 219.39		555.24 (245.9)	599.58 ± 214.94		**<.001**
IGF-1 (nmol/L)							
Total sample (n = 101)	15.14 (9.94)	16.36 ± 7.74		9.4 (8.34)	11.22 ± 6.08		**<.001**
Delirium (n = 37)	13.26 (9.97)	18.12 ± 7.58	.477	10.03 (9.01)	13.39 ± 5.94	.639	**<.001**
No delirium (n = 64)	15.77 (9.89)	16.8 ± 7.86		9.08 (8.06)	11.12 ± 6.2		**<.001**

Abbreviations: IQR, inter-quartile range; SD, standard deviation; IGF-1, Insulin-like growth factor 1.
[a] Mann-Whitney test.
[b] Wilcoxon test.
Bold values correspond to *P* value < .05.

patients had a plasma elevation of IGF-1 levels following surgery. This response profile was significantly more common in patients who developed delirium (24.3% vs 7.8%; $\chi^2(1) = 5.354$; $P = .034$) and was not explained by preoperative differences ($U = 476.5$; $W = 581.5$; $P = .193$; Figure 1D). No correlation was found between preoperative hemoglobin levels and the IGF-1 change after surgery (data not shown).

Inflammatory Response and Neuroendocrine Axes

The magnitude of the elevation of plasma cortisol levels following surgery ($cortisol_{post/pre}$) correlated with ΔIL-6 ($P = .485$; $P = .002$), ΔIL-8 ($P = .429$; $P = .008$), and ΔIL-10 ($P = .544$; $P < .001$) in patients with delirium. There were no such correlations in patients devoid of postoperative delirium. The magnitude of IGF-1 change following surgery ($IGF\text{-}1_{post/pre}$) correlated with ΔCRP both in patients with ($P = -.477$; $P = .003$) and without ($P = -.345$; $P = .005$) delirium.

Discussion

In this study, we explored the contribution of 2 neuroendocrine axes to postoperative delirium pathophysiology in patients undergoing elective hip arthroplasty. We found that delirium was associated with a more pronounced elevation in the cortisol plasma levels and a less frequent suppression of plasma levels of IGF-1 after surgery. In order to capture early changes in plasma biomarkers and mental state, all participants were assessed for the presence of delirium in the early postoperative period (on the evening of the surgery day) and reassessed in the following 2 days. This intensive monitoring of the mental state may have contributed to the higher incidence of delirium in our participant (36.6%) compared to similar samples (3.6%-28.3%).[39]

Tissue destruction and insults (eg, hypotension, hypoxia, pain, blood loss, anesthesia, and drugs) elicit production and release of inflammatory mediators, both at the periphery and in the brain with subsequent activation of the HPA axis and descendent sympathetic fibers.[40] Cortisol, norepinephrine, and other endocrine mediators, including IGF-1, regulate the actions of proinflammatory cytokines providing a bidirectional interaction between the 2 systems.[5] Consistent with the essential role of both the immune system and the HPA axis in the adaptive response to surgery, we observed a generalized postoperative elevation of plasma cytokines and cortisol levels in relation to their baseline levels. The inflammatory response

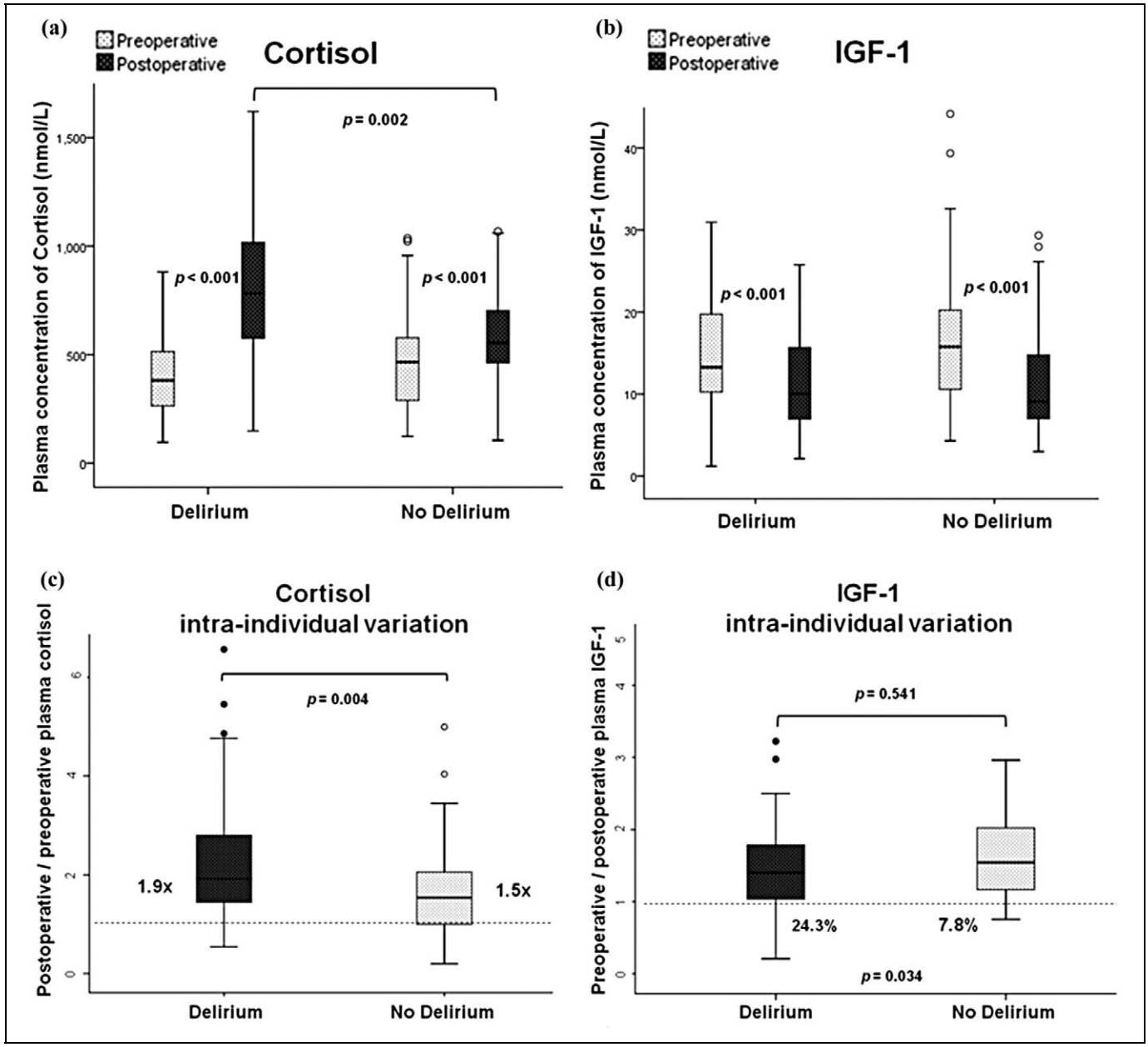

Figure 1. Plasma levels of cortisol (A) and insulin-like growth factor 1 (B) in patients with and without delirium before and after surgery with intraindividual variation in relation to baseline levels (C and D).

to surgery in both delirium and nondelirium patients was tightly coordinated as shown by the strong correlation in the expression of most inflammatory mediators. Thus, the increase in IL-6 and IL-8 was associated with a concomitant increase in IL-10, denoting the existence of a counterregulatory effect of IL-10 on IL-6 levels, as demonstrated in a recent study.[41] The surgery induced an overall reduction in IGF-1 plasma levels, reflecting the suppression of GH/IGF-1 in response to a diversity of surgical procedures[42-44] or anesthesia.[45] The magnitude of IGF-1 change ($IGF\text{-}1_{post/pre}$) correlated with ΔCRP both in patients with ($P = -.489$; $P = .002$) and without ($P = -.375$; $P = .002$) postoperative delirium, suggesting a close association between the acute inflammatory response and IGF-1 reduction. In contrast to studies reporting low IGF-1 in medically ill patients with delirium,[25-27] we found no association between preoperative IGF-1 levels and occurrence of postoperative delirium, similar to the 2 recent studies.[28,29]

The association between hemoglobin levels and delirium is largely underinvestigated. While one study reported anemia as a risk factor for delirium in medically ill patients,[46] another one failed to find any relation.[47] In our study, patients who developed postoperative delirium had lower hemoglobin levels prior to their surgery. Preoperative hemoglobin levels have been found to be inversely correlated to postoperative morbidity and mortality rates.[48] One possible mechanism by which lower hemoglobin levels can be directly related to delirium is a

decreased oxygen distribution in the CNS, even when its saturation remains elevated during surgery. Also, preoperative anemia is a major indication for perioperative blood transfusion, and both factors have been independently associated with increased mortality, ischemia, and infections.[49] In our study, patients with lower preoperative levels of hemoglobin were more likely to receive blood transfusions, suggesting that this procedure may also be linked to the occurrence of postoperative delirium. This can explain why patients who developed delirium had higher postoperative levels of hemoglobin than patients without delirium.

In the present study, although plasma cortisol and cytokine levels were similar preoperatively in delirium and nondelirium groups, patients who developed delirium had a higher magnitude of plasma cortisol elevation after surgery (1.9- vs 1.5-fold; $P = .004$). Possible pathophysiological mechanisms underlying this "aberrant stress response"[15] might involve (i) a higher burden of "stressful" stimuli related to the surgical procedure itself and/or as intra- and postoperative factors; (ii) an abnormally intense inflammatory reaction; (iii) exaggerated response of the HPA axis to normal levels of inflammatory mediators; or (iv) inefficient inhibitory regulation of the HPA axis with failure of a prompt poststress return of cortisol to basal levels. The exact mechanisms will need to be determined in future studies.

Although we could not demonstrate statistical significance, patients with delirium did show some trends of increased surgical stress (ie, more frequent blood transfusion and higher surgery duration), which could have elicited more robust inflammatory and HPA responses. Indeed, a higher magnitude of leukocyte count elevation, as observed in patients with delirium, has been related to the burden of surgical stress[50] as a primary response to trauma. It is well known that IL-6 stimulates the release of corticotrophin releasing factor from the CNS, the release of adrenocorticotropic hormone (ACTH) from the pituitary gland, and the release of cortisol from the adrenal gland.[51] Moreover, increased IL-6 is at least in part responsible for maintaining the elevated cortisol in plasma through ACTH-independent secretion under stressful conditions.[52,53] It is unlikely that the higher cortisol increase observed in our patients with delirium could be subsequent to an abnormally intense inflammatory reaction since the postoperative plasma levels of inflammatory mediators were identical in both groups. On the other hand, older people undergoing abdominal surgery, who develop confusion have been reported to show higher plasma cortisol and IL-6 levels and a more sustained correlation between both biomarkers during the early postoperative period than in nondelirium patients.[54] Similarly, we observed a correlation between the plasma cortisol response and ΔIL-6, ΔIL-8, and ΔIL-10 only in patients who developed postoperative delirium, but not in controls, suggesting a state of HPA axis hyperresponsiveness to acute stress in patients who developed postoperative delirium. Hyperactivity of the HPA axis, with increased adrenal sensitivity to ACTH, has been documented in patients with dementia.[55] Furthermore, there is evidence that the sensitivity of the HPA axis to negative feedback by cortisol decreases with aging[17,56,57] and with dementia severity,[58] leading to a slower recovery from acute stress. This can be a result of several factors including a decrease in the hippocampal corticosteroid receptor density[59] and changes in the CSF steroid concentrations.[60] Importantly, patients with dementia who exhibit a deficient cortisol suppression to dexamethasone were found to be more likely to develop delirium.[58] It is therefore possible that a certain degree of hyperactivity of the HPA axis following acute stress and/or impaired HPA axis sensitivity toward the negative steroid feedback contributes to an exaggerated cortisol response in patients who develop postoperative delirium. The mechanisms by which high levels of corticosteroids are related to delirium symptoms remain unclear, although a direct negative impact on cognition, with impaired declarative and working memory, has been demonstrated.[61]

Plasma levels of baseline IGF-1 did not discriminate between patients with and without postoperative delirium, and the surgical intervention inducing a comparable reduction of this biomarker in both groups. However, in a minority of cases, IGF-1 levels increased in relation to baseline, and this was significantly more frequent in the delirium group (24.3% vs 7.8%; $P = .034$). Importantly, both profiles (suppressors and enhancers) showed identical preoperative IGF-1 levels suggesting differential abilities to respond to the perioperative factors rather than inherent differences in activation status of the GH/IGF-1 axis before surgery. Several studies demonstrate that acute reduction in the IGF-1 plasma levels reflects the suppression of the GH/IGF-1 axis in response to acute stress. Although central production of GH is increased, probably due to the absence of somatostatin and lack of inhibitory feedback of IGF-1,[25] GH receptor availability is reduced in peripheral organs[43,62] together with a nitric oxide—mediated reduction of hepatic *IGF-1* gene transcription.[62,63] Simultaneously, circulating levels of IGF-binding proteins are affected by the combined action of several factors including insulin, glucagon, catecholamines, and cytokines, which ultimately affects the half-life of IGF-1.[45] Whether activation of the immune system and the subsequent expression of proinflammatory cytokines decrease IGF-I activity in the brain is unknown. However, there is evidence that administration of IGF-1 in the CNS reduces the expression of central inflammatory mediators and increases the expression of brain-derived neurotrophic factor.[64] Taken together these data suggest that disturbances in regulatory mechanisms of the GH/IGF-1 axis may be associated with postoperative delirium.

The strength of this prospective study was the ability to assess patients before the exposure to multiple perioperative risk factors for delirium and to observe the individual patterns of change in several biological markers in relation to their mental state and delirium status. However, although the biomarkers were measured only at 1 time point following surgery, the clinical status was determined during 3 consecutive assessments that were not coincident with the blood draw. Given this temporal mismatch, the reported associations between biomarker changes and delirium should be interpreted cautiously. In addition, in the current study we have largely concentrated on the

measures of the HPA axis and IGF-1, not addressing additional blood peripheral measures[34,35] or relating them to delirium severity or analgesic drug regimes. Similarly, the current study was conducted on cognitively intact participants, thus limiting the value of our findings to older adults without dementia. Another limitation of our study, shared by a number of similar studies in this field on peripheral delirium biomarkers, is that biomarkers measured from peripheral blood do not necessarily reflect the brain levels. These limitations need to be addressed in future studies with serial blood assessments (eg, before, during, and after delirium) coupled with determination of cerebrospinal fluid levels.[65] Since detailed neuropathological studies on delirium are lacking,[66,67] the current neurobiological understanding of the pathogenesis of delirium is based largely on correlative clinicobiochemical studies. Despite obvious biases, the design of the current study is considered to be a useful way to generate etiological hypothesis, although causal effects are not possible to determine.[68]

In summary, our study provides evidence that the acute and transient failure of brain function underlying delirium is associated with dysfunction of 2 neuroendocrine axes indicative of HPA axis hyperresponsiveness and less frequent suppression of the GH/IGF-1 axis response to acute stress. Considerable interest exists whether modulation of these pathways can provide new approaches to the prevention and treatment of delirium.

Authors' Note

J.C., V.N., and P.B. contributed in the acquisition of data for the study and preparation of the manuscript. J.C., A.V.-S., and E.B.M.-L. were responsible for the study concept and design as well as for the analysis and interpretation of data.

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Declaration of Conflicting Interests

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