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A pilot investigation of the association of genetic polymorphisms regulating corticotrophin-releasing hormone with posttraumatic stress and depressive symptoms in medical-surgical intensive care unit survivors ☆,☆☆

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ABSTRACT

Purpose: To determine if single nucleotide polymorphisms of the corticotrophin-releasing hormone binding protein (CRHBP, rs10055255) and CRH receptor type 1 (*CRHR1*, rs1876831) were associated with posttraumatic stress disorder (PTSD) and depressive symptoms following medical-surgical intensive care unit (ICU) hospitalization.

Materials and Methods: We extracted DNA for genotyping from saliva samples of 93 ICU patients enrolled in a prospective cohort investigation. Follow-up interviews conducted 3 and 12-months post-ICU included assessment of PTSD symptoms with the PTSD Checklist-Civilian Version and depressive symptoms with the Patient Health Questionnaire–9.

Results: Homozygosity for the CRHBP rs10055255 T allele was associated with significantly fewer post-ICU PTSD ($\beta = -10.8$, 95% confidence interval [95% CI], −17.7 to −3.9; $P = .002$) and depressive symptoms ($\beta = -3.7$, 95% CI, −6.7 to −0.7; $P = .02$). Carrying a *CRHR1* rs1876831 C allele was associated with significantly more post-ICU depressive symptoms compared to T/T homozygotes (C/T heterozygtes: $\beta = 6.9$, 95% CI, 1.2-12.6; $P = .02$; C/C homozygotes: $\beta = 5.8$; 95% CI: 0.2-11.3; $P = .04$). These associations remained significant after adjustment for age, race, illness severity, and in-ICU steroid exposure.

Conclusions: Despite a small sample size, our findings suggest a potential role for genetic variants of CRHBP and *CRHR1* in the development of post-ICU psychiatric morbidity.

1. Introduction

Advances in critical care medicine have led to increasing survival rates for the millions of patients hospitalized annually in intensive care units (ICUs) for the treatment of critical illnesses [1]. As interest has grown in quality of survivorship following critical illnesses, an emerging body of literature has established that critical illness survivors may face substantial mental health morbidities. Three systematic reviews of 24 studies of general ICU and acute respiratory distress syndrome (ARDS) survivors have identified that 22% and 28% of critical illness survivors have substantial posttraumatic stress disorder (PTSD) and depressive symptoms, respectively [2–4]. High rates of these psychiatric disorders among critical illness survivors are an important public health concern since PTSD and major depression have been shown to be independently associated with risk of adverse medical outcomes and increased healthcare costs [5–7].

Although psychiatric morbidity in critical illness survivors has become increasingly recognized, relatively little is known about the etiology of these adverse post-ICU outcomes. Increased understanding of the mechanisms by which psychiatric disorders may develop in the aftermath of critical illnesses could lead to the development of candidate biomarkers that may identify patients at greatest risk for these outcomes.

One potential common pathway between critical illnesses and psychiatric disorders such as PTSD and major depression is the hypothalamic-pituitary-adrenal (HPA) axis [2]. Critical illnesses have been shown to induce multiple changes in cortisol homeostasis across all aspects of the HPA axis [8]. Furthermore, HPA axis hyperactivity, particularly involving corticotrophin-releasing hormone (CRH), has been theorized to play a key role in the etiology of mood and anxiety disorders [9]. Single-nucleotide polymorphisms

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(SNPs) of the corticotrophin-releasing hormone receptor type 1 (*CRHR1*) gene have been shown to be associated with risk of PTSD and major depression in the context of extreme stress [10,11]. In addition, SNPs of the corticotrophin-releasing hormone binding protein (CRHBP) gene have been shown to be associated with antidepressant response and remission of depressive symptoms [9]. However, no studies in non-injured critical illness survivors have examined the role that these important genetic variants may play in the pathogenesis of post-ICU PTSD and depressive symptoms.

The present longitudinal pilot investigation sought to determine if the CRHBP (rs10055255) and *CRHR1* (rs1876831) SNPs were associated with risk of PTSD and depressive symptoms following medical-surgical intensive care unit (ICU) hospitalization. We hypothesized that these SNPs would have significant associations with risk of both post-ICU PTSD and depressive symptoms and that these associations would remain present after controlling for age, race and illness severity at ICU admission.

2. Methods

2.1. Study setting and participants

Our study cohort came from a larger prospective investigation of psychiatric and cognitive outcomes following medical-surgical ICU admission. The details of the parent study have been previously described [12]. Briefly, 150 patients admitted to an ICU for over 24 hours were prospectively recruited between September 2010 and July 2011. Key exclusion criteria were (1) initial admission diagnosis of traumatic injury, (2) pre-existing cognitive impairment or dementia diagnosis noted in the medical record, (3) communication/language barrier, (4) ICU length of stay $\leq$24 hours, (5) pre-existing medical illness with life-expectancy of $<$12 months, and (6) admission for a suicide attempt. The study protocol was approved by the University of Washington Institutional Review Board, and all participants provided informed consent for all aspects of the study protocol prior to enrollment.

The present study included 93 patients who provided saliva samples for DNA analyses. Saliva samples were obtained from consented patients prior to hospital discharge. There were no significant differences in baseline or clinical characteristics between the 93 patients who provided saliva samples and the other 57 patients from the parent study that did not provide a sample. Enrolled patients completed an in-person interview prior to hospital discharge and were re-interviewed via telephone at 3 and 12 months post-ICU.

2.2. Measurements and assessments

2.2.1. PTSD symptoms

PTSD symptoms at 3 and 12-months post-ICU were assessed with the PTSD Checklist–civilian version (PCL-C) [13]. The PCL-C includes questions regarding 5 symptoms in the intrusive symptom cluster (eg, intrusive thoughts, nightmares), 7 symptoms in the avoidant symptom cluster (eg, avoidance of thoughts or activities that remind the patient of the stressor, emotional numbing), and 5 symptoms in the arousal symptom cluster (eg, impaired sleep, hypervigilance), and symptom severity is rated on a 5-point Likert scale [13]. Substantial PTSD symptoms can be ascertained with the PCL-C by following an algorithm that considers a score of 3 or more on at least 1 intrusive symptom, 3 avoidant symptoms, and 2 arousal symptoms as consistent with *DSM-IV* diagnostic criteria [13].

2.2.2. Depressive symptoms

Depressive symptoms at 3 and 12-months post-ICU were assessed with the Patient Health Questionnaire–9 (PHQ-9) [14]. We defined substantial depressive symptoms as a PHQ-9 score $\geq$10. The PHQ-9 threshold score of 10 or more for a probable case of major depression has been found to have high sensitivity (88%) and specificity (88%) for the diagnosis of major depression compared to a structured psychiatric interview [14].

2.3. Patient and ICU-related characteristics

Baseline patient characteristics and ICU clinical factors were obtained through medical record review and in-person interviews. Medical record-obtained characteristics included demographics (e.g., age, sex, race), ICU admission diagnosis, baseline medical comorbidity information to compute a Charlson Comorbidity Score [15], illness severity measures at ICU admission to compute a Simplified Acute Physiology Score II (SAPS II) [16], ICU length of stay, requirements for mechanical ventilation and duration of ventilation, requirement for major surgery or blood product transfusion, days of in-ICU exposure to benzodiazepine, opioid, and corticosteroid medications, presence of delirium in-ICU per nursing documented assessment using the confusion assessment method–ICU (CAM-ICU) [17], and presence of confusion/disorientation/difficulty following commands in critical care nursing documentation. We defined probable delirium as a documented positive CAM-ICU assessment in the ICU or nursing documented presence of confusion/disorientation/difficulty following commands at any point in the ICU.

Additional patient characteristics obtained from the baseline interviews included demographic data not obtained from medical records (eg, marital/partnered status, education); assessment of prior trauma exposure with the National Comorbidity Survey-Replication Trauma History Screen [18], and lifetime history of major depression with the MINI International Neuropsychiatric Interview (MINI) major depressive episode module [19].

2.4. Sample collection and genotyping

Saliva samples were obtained from patients at the time of the in-hospital baseline interview using Oragene saliva collection kits (DNA Genotek, Ontario, Canada) and extracted following the manufacturer's protocol. DNA samples were quantified and checked for quality on a NanoDrop instrument (Thermo Scientific, DE, USA). SNPs were genotyped using a StepOnePlus Real-Time PCR System and TaqMan SNP Genotyping Assays (Applied Biosystems, CA); 50 ng genomic DNA was amplified in the presence of gene-specific primers and allele-specific fluorescent probes following the manufacturer's instructions. Genotypes were called using TaqMan Genotyper software.

2.5. Statistical analysis

We present descriptive data as medians and interquartile ranges (IQRs) or proportions. We used χ^2 tests to examine if there were deviations from Hardy-Weinberg equilibrium among the CRHBP (rs10055255) and *CRHR1* (rs1876831) SNPs and found no deviations. To examine if there were significant differences in patient or clinical characteristics by CRHBP or *CRHR1* genotype, we used χ^2 tests or Fisher exact tests for categorical variables and non-parametric K-sample equality-of-medians tests for continuous variables.

In order to test our hypotheses of interest, we used mixed-model linear regression analyses. We constructed separate general genetic models for CRHBP and *CRHR1*. In our analyses we retained the 3 distinct genotype classes for each gene as independent categorical variables, i.e., making no assumptions about how the risk for heterozygotes compares with the 2 homozygotes. Dependent variables were the repeated measures of PTSD symptoms and depressive symptoms in 2 separate regression models. Initially, we tested the associations of the CRHBP and *CRHR1* genotypes with our outcomes of interest without adjustment. We then repeated our regressions and adjusted for age, race, and SAPS II scores. We implemented our regression analyses using *xtmixed* in STATA 12 (Stata Corp, College