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Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11 World Trade Center attacks

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ABSTRACT

Background: Systemic inflammation has emerged as a promising marker and potential mechanism underlying post-traumatic stress disorder (PTSD). The relationship between posttraumatic stress pathology and systemic inflammation has not, however, been consistently replicated and is potentially confounded by comorbid illness or injury, common complications of trauma exposure.
Methods: We analyzed a large naturalistic cohort sharing a discrete physical and mental health trauma from the destruction of the World Trade Center (WTC) towers on September 11, 2001 (n = 641). We evaluated the relationship between multiple physical and mental health related indices collected through routine evaluations at the WTC Environmental Health Center (WTC EHC), a treatment program for community members exposed to the disaster. C-Reactive Protein (CRP), a marker of systemic inflammation, was examined in relation to scores for PTSD, PTSD symptom clusters (re-experiencing, avoidance, negative cognitions/mood, arousal), depression and anxiety, while controlling for WTC exposures, lower respiratory symptoms, age, sex, BMI and smoking as potential risks or confounders.
Results: CRP was positively associated with PTSD severity ($p < 0.001$), trending toward association with depression ($p = 0.06$), but not with anxiety ($p = 0.27$). CRP was positively associated with re-experiencing ($p < 0.001$) and avoidance ($p < 0.05$) symptom clusters, and trended toward associations with negative cognitions/mood ($p = 0.06$) and arousal ($p = 0.08$).
Conclusions: In this large study of the relationship between CRP and posttraumatic stress pathology, we demonstrated an association between systemic inflammation and stress pathology (PTSD; trending with depression), which remained after adjusting for potentially confounding variables. These results contribute to research findings suggesting a salient relationship between inflammation and post-traumatic stress pathology.

1. Introduction

Systemic inflammation has emerged as a potential biological mechanism in the pathogenesis of posttraumatic stress disorder (PTSD) (Baker et al., 2012; Passos et al., 2015) and depression (Haroon et al., 2012; Miller et al., 2009), the two most common and

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highly comorbid posttraumatic stress responses (Flory and Yehuda, 2015; Galatzer-Levy et al., 2013; Kessler et al., 2005). Elevated levels of C-reactive protein (CRP), a pro-inflammatory acute phase protein that can be measured systemically, have been associated with both PTSD and depression (Gill et al., 2009; Howren et al., 2009; Valkanova et al., 2013), including in populations exposed to terrorism (Canetti et al., 2014). Variants of the CRP gene are also associated with PTSD (Michopoulos et al., 2015), and elevated CRP levels prior to trauma are associated with the development of PTSD prospectively (Eraly et al., 2014).

Post traumatic stress pathology is heterogeneous (Galatzer-Levy and Bryant, 2013) and symptoms of PTSD have been divided into four clusters reflecting these diverse components including symptoms of re-experiencing, avoidance, negative alterations in cognitions and mood (negative cognitions/mood), and alterations in arousal and reactivity (arousal). These components are supported by factor-analytic studies (Cox et al., 2002; Marshall et al., 2013) and have been adopted for the DSM-V criteria.

Elevated CRP levels have been reported in association with re-experiencing symptoms of PTSD (Canetti et al., 2014; Miller et al., 2001; von Känel et al., 2007), and recently, with arousal symptoms (Michopoulos et al., 2015). This growing body of research suggests that systemic inflammation may be a biological marker and participate in the development or persistence of posttraumatic stress responses. The mammalian response to danger and stress involves the rapid activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA-axis). This axis interacts with inflammatory pathways and may be a link between inflammation and PTSD (Baker et al., 2012; Michopoulos et al., 2017). Despite this potential overlap, the data supporting a relationship between CRP and PTSD have not consistently been replicated; both high and low CRP levels or no association with PTSD have been reported (McCanlies et al., 2011; Söndergaard et al., 2004; von Känel et al., 2007). The inconsistency of findings may relate to small sample sizes, the use of cross sectional data, or variable trauma exposures. Further, key factors that are associated with both inflammation and trauma, including injury and illness, have not been accounted for in existing studies.

The current study tested the hypothesis that elevated CRP was associated with posttraumatic stress pathology, including PTSD symptom clusters, depression and anxiety, controlling for WTC exposures, lower respiratory symptoms, age, sex, BMI and tobacco use. We used a large civilian population exposed to the terrorist attack on the World Trade Center (WTC) towers and its ensuing environmental disaster. These patients were enrolled in the WTC Environmental Health Center (WTC EHC), a treatment and monitoring program for physical and psychological effects associated with the attacks (Reibman et al., 2009, 2016). Individuals had potential for acute environmental exposures to the initial dust clouds created as the WTC buildings collapsed (WTC dust cloud), as well as chronic inhalation and topical exposure from re-suspended dust and fumes from prolonged fires (Lioy and Georgopoulos, 2006; Lippmann et al., 2015; Maslow et al., 2012; Reibman et al., 2016). Adverse health effects in community members (residents, local workers, clean-up workers, and others) include upper and lower respiratory symptoms (Brackbill et al., 2009; Farfel et al., 2008; Friedman et al., 2013; Lin et al., 2007; Reibman et al., 2005). In addition, many individuals witnessed death and dismemberment and often experienced their own fear of death as they escaped collapsing buildings or engulfment by blinding dust clouds. Some individuals were exposed to extended rescue and recovery efforts or displacement from homes and workplaces due to clean up efforts.

2. Methods

2.1. Subjects

The Bellevue Hospital Center WTC EHC provides medical and mental health treatment for self-referred community members (Reibman et al., 2009, 2016). Well-described adverse health effects in this population include persistent lower respiratory symptoms (LRS) (Brackbill et al., 2009; Farfel et al., 2008; Friedman et al., 2013; Lin et al., 2005, 2007; Reibman et al., 2005). Mental health symptoms include those associated with PTSD, depression, and anxiety (Brackbill et al., 2009; DiGrande et al., 2008). The Institutional Review Board of New York University School of Medicine approved the research database (NCT00404898) and only data from patients who signed informed consent were used for analysis. CRP measurements were performed in patients undergoing initial evaluation or monitoring between August 2007 and December 2012. Patients were included in the analysis if they also had complete exposure information, and complete medical and mental health questionnaires.

2.2. Measures

Upon enrollment in the WTC EHC, patients completed a multidimensional, interviewer-administered questionnaire that included demographic information, characterizations of WTC-related exposure, and tobacco use (Reibman et al., 2009). Individuals were classified as positive for dust cloud exposure if they reported having been in a WTC dust cloud created by the collapsing buildings on 9/11/2001. Potential for WTC acute and chronic exposures were characterized by classification into four additional categories: local resident (resident), local worker, clean-up worker, other. Patients who reported more than 5 pack-year history of tobacco use were defined as smokers. The presence and severity of LRS of wheeze, cough, chest tightness and dyspnea were measured by standardized health questionnaires (Reibman et al., 2009) and patients with symptoms more than twice per week during the month preceding enrollment were considered positive for persistent LRS. In addition, body mass index (BMI) of patients were calculated using information gathered during the initial medical visit.

2.2.1. CRP

CRP was measured using a wide-range CRP assay (Siemen's Diagnostic Center, Tarrytown, NY). The wide range CRP (wr-CRP) assay is a clinically used measure that has a wide sensitivity range with a lower limit of detection of 0.12 mg/L. The wr-CRP correlates significantly with the high sensitivity CRP (hs-CRP) measurements and quantitation of microinflammatory activity in individuals (Rogowski et al., 2005). A value > 3 mg/L was considered “High” (Yeh and Willerson, 2003).

2.2.2. Psychiatric symptom assessments

2.2.2.1. Posttraumatic stress disorder symptoms. The Post-traumatic Check List-17 (PCL-17) (Weathers FW et al., 1993), was used to measure PTSD symptom presence and severity. A score ≥ 44 was used to suggest “probable PTSD” (PTSD) (Farfel et al., 2008). Questions from the PCL-17 were matched to the DSM-V diagnostic criteria for characterization into four clusters reflecting symptoms of re-experiencing, avoidance, negative alterations in cognitions and mood (negative cognitions/mood), and alterations in arousal and reactivity (arousal), and an average score was calculated for each cluster, ranging between 1 and 5.

2.2.2.2. Depression and anxiety. We used the Hopkins Symptom Checklist for depression and anxiety (HSCL-25) (Derogatis et al.,