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One airway: Biomarkers of protection from upper and lower airway injury after World Trade Center exposure☆

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Summary
Background: Firefighters exposed to World Trade Center (WTC) dust have developed chronic rhinosinusitis (CRS) and abnormal forced expiratory volume in 1 s (FEV_1). Overlapping but distinct immune responses may be responsible for the clinical manifestations of upper and lower airway injury. We investigated whether a panel of inflammatory cytokines, either associated or not associated with WTC-LI, can predict future chronic rhinosinusitis disease and its severity.
Methods: Serum obtained within six months of 9/11/2001 from 179 WTC exposed firefighters presenting for subspecialty evaluation prior to 3/2008 was assayed for 39 cytokines. The

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main outcomes were medically managed CRS ($N = 62$) and more severe CRS cases requiring sinus surgery ($N = 14$). We tested biomarker-CRS severity association using ordinal logistic regression analysis.
Results: Increasing serum IL-6, IL-8, GRO and neutrophil concentration reduced the risk of CRS progression. Conversely, increasing TNF-α increased the risk of progression. In a multivariable model adjusted for exposure intensity, increasing IL-6, TNF-α and neutrophil concentration remained significant predictors of progression. Elevated IL-6 levels and neutrophil counts also reduced the risk of abnormal FEV_1 but in contrast to CRS, increased TNF-α did not increase the risk of abnormal FEV_1.
Conclusions: Our study demonstrates both independent and overlapping biomarker associations with upper and lower respiratory injury, and suggests that the innate immune response may play a protective role against CRS and abnormal lung function in those with WTC exposure.

Abbreviations

CRS	chronic rhinosinusitis
FDNY	Fire Department City of New York
FEV_1	forced expiratory volume in 1 s
GRO	growth-regulated oncogene
IL-6	interleukin-6
IL-8	interleukin-8
LLN	lower limit of normal
MME	medical monitoring entry
NHANES	National Health and Nutrition Examination Survey
PFT	pulmonary function test
PM	particulate matter
PMN	polymorphonuclear neutrophil
SPE	subspecialty pulmonary evaluation
TNF-α	tumor necrosis factor-alpha
WTC	World Trade Center
WTC-LI	World Trade Center-related lower airway injury

Introduction

The World Trade Center (WTC) collapse produced vast quantities of respirable dust affecting Fire Department of New York (FDNY) rescue workers, other exposed workers, lower Manhattan residents and children [1—6]. WTC dust was alkaline (pH, 9.2—11.5) and was comprised of metals, radionuclides, ionic species, asbestos, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzodioxines and other potentially hazardous materials. The bulk of WTC particulate matter (PM) was larger than 10 μm, which usually is filtered in the nasopharynx [7]. However, the body's usual protective barriers were overwhelmed, producing intense dust exposure to both the upper and lower airways [2].

A high incidence of upper and lower airway respiratory disorders has persisted in WTC exposed firefighters years after 9/11 [8]. Chronic rhinosinusitis (CRS) has been the most common manifestation of upper airway injury in this population. Prior to 9/11, only 4.4% of FDNY firefighters reported rhinosinusitis symptoms. By one year after 9/11, self-reported rhinosinusitis symptoms had increased 10-fold (45.1%) and persisted above 30% well into the fifth year after 9/11 [9,10]. Numerous disability claims arising from respiratory disorders such as CRS have had substantial financial ramifications [11].

Shared upper and lower airway immune response is well established in the spectrum of atopic rhinosinusitis and allergic asthma [12—14] and as a cause of chronic cough syndrome [15]. CRS in the FDNY firefighter cohort exists both in isolation and in accompaniment with WTC lower airway injury (WTC-LI) [16], portending overlapping but distinct immune pathogenesis of irritant-induced upper and lower airway injury. The pathophysiology of CRS after occupational irritant exposure has not been well characterized.

We have previously reported inflammatory biomarkers that are predictive of future abnormal lung function in the FDNY firefighter cohort [17]. No biomarker studies have been published that predict the long-term outcome of upper airway disease in this population. We investigated whether a panel of inflammatory cytokines, either associated or not associated with WTC-LI, can predict future chronic rhinosinusitis disease and its severity.

Methods

Study design

All WTC exposed FDNY workers were enrolled in the Medical Monitoring and Treatment Program. FDNY workers ($N = 1720$) who complained of any respiratory symptoms between October 1, 2011 and March 10, 2008 were systematically sent for subspecialty pulmonary evaluation (SPE). We performed a nested case—cohort study on firefighters using this baseline cohort of 1720 exposed, symptomatic workers. Study subgroups were derived from the baseline cohort after excluding for patients with prior lung or sinus disease. Fig. 1. Chronic rhinosinusitis (CRS) in our study was defined as nasal and/or sinus inflammation, with