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Cough and Wheeze Events Are Temporally Associated with Increased Pain in Individuals with Sickle Cell Disease without Asthma

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Human clinical studies and murine models suggest that pulmonary inflammation is an intrinsic component of sickle cell disease (SCD) (Field *et al*, 2011, Morris *et al*, 2003, Nandedkar *et al*, 2008, Pawar *et al*, 2008, Pritchard *et al*, 2012, Pritchard *et al*, 2004) and a growing body of retrospective and cross-sectional studies demonstrates that symptoms, such as cough or wheeze, often occur without asthma and are associated with increased SCD complications (pain, acute chest syndrome and death) (Cohen *et al*, 2011, Field *et al*, 2011, Glassberg *et al*, 2012). To better understand the incidence of respiratory symptoms over time, and to identify the percentage of individuals without asthma who could potentially benefit from pulmonary-anti-inflammatory therapy, we conducted a prospective, longitudinal cohort study of individuals with SCD who do not have asthma.

This was an institutional review board-approved, longitudinal cohort study conducted between 6 January 2012 and 7 November 2013. We included individuals with SCD aged over 15 years. Exclusion criteria were asthma (a prospective multi-step algorithm screened out all cases of confirmed or possible asthma) and pregnancy. Individuals were interviewed

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approximately every 8 weeks for the presence of respiratory symptoms and SCD complications with validated questionnaires.

The primary hypothesis was that time periods during which respiratory symptoms were reported would be associated with increased rates of acute SCD pain. Because each participant contributed multiple observations to the data, we used a generalized estimating equation for the primary analysis with adjustment for patient-level clustering. The predictor variable was the presence of wheeze or cough over the last 2 months (yes/no) and the outcome variable was the number of visits to the emergency department (ED) during the next follow-up period. Visits for pain less than 72 h apart were considered part of the same pain episode. Definitions of all study variables were generated *a priori* and adhered to established definitions (Ballas *et al*, 2010).

A total of 69 individuals consented: 19 (27.5%) were not included because asthma could not be excluded, and three were lost to follow-up. Characteristics of the 47 remaining participants are listed in Supplemental Table I. The mean length of follow-up was 281 days (min 14 days, max 573 days). 170 surveys were performed on the 47 participants with a mean length of 69 days between surveys. A mean of 3.62 surveys (standard deviation 1.7, range 1–7) were administered to each participant. There were no deaths.

Consistent with prior cross-sectional data (Cohen *et al*, 2011, Field *et al*, 2011, Knight-Madden *et al*, 2013), the proportion of individuals with active respiratory symptoms at any time was approximately 20%. However, the proportion increased with increasing duration of follow-up. By the end of our study, the proportion of participants who reported cough or wheeze at least once during follow-up was 68% (Figure 1). The majority (65.2%) reported cough or wheeze with colds whereas only 19.1% reported cough or wheeze without a cold.

There were 224 ED visits in total and 210 ED visits for pain during the 36.2 person-years of follow-up (5.8 ED visits per patient-year). In the adjusted model, the rate of ED visits for pain was approximately double (Relative risk [RR] 1.96, 95% confidence interval [CI] 1.17 – 3.29) during time periods in which participants reported symptoms of cough or wheeze. There were 120 admissions to the hospital for pain and the difference between periods with and without cough or wheezing was not statistically significant (RR 1.99, 95% CI 0.96 – 4.10, $p = 0.06$). There were 6 episodes of acute chest syndrome and 4 episodes of pneumonia during the sample period. Differences in admission rates for acute chest syndrome (RR 3.44, 0.93 – 12.80, $p = 0.06$) and pneumonia (RR 2.45, 95% CI 0.35 – 17.05, $p = 0.37$) were not statistically significant.

With this prospective longitudinal cohort study - the first to systematically exclude asthma - we report the frequency and timing of respiratory symptoms in individuals with SCD who do not have asthma and identify a temporal relationship between respiratory symptoms and SCD pain. The frequency of respiratory symptoms is dramatically higher than our group previously reported using retrospective data (12.1% vs. 68% in the current study) (Glassberg *et al*, 2012) and consistent with prior cross-sectional and retrospective studies that demonstrated increased SCD morbidity for individuals who report a history of wheezing. More importantly, our data indicate that over time, the majority (68% in our sample) of

individuals without asthma will have cough or wheeze and that even mild symptoms are associated with more SCD pain. While inhaled corticosteroids are already standard of care for individuals with asthma and SCD, prospective trials are indicated to determine if therapies to reduce pulmonary inflammation have clinical benefit for people with SCD that do not have asthma. The majority of cough and wheeze (65%) in this study was reported in the setting of, or after presumed viral upper respiratory infection, suggesting that this may be a particularly beneficial time to try inhaled corticosteroids. It is also important to consider whether cough and wheeze are proximal events that lead to impaired oxygenation of the blood and downstream vaso-occlusion, or rather results of the global worsening of the inflammatory milieu causing red cell sickling and vaso-occlusion (in which case, pulmonary anti-inflammatory therapy would likely be ineffective).

This study has important limitations. The sample was small, which limited our ability to perform more complex analyses on the data, such as assessment for trends in morbidity with increased frequency and severity of respiratory symptoms. Additionally, it is possible that not all asthma diagnoses were correctly classified. However, this potential selection bias would both favour the null hypothesis and minimize the likelihood that individuals with asthma were included in the cohort.

In conclusion, this prospective longitudinal study demonstrates higher cumulative rates of cough and wheeze than previous cross-sectional data. Clinicians should be aware of the temporal relationship between respiratory symptoms and SCD morbidity, and that a period of cough or wheeze may herald an acute care visit for pain. Clinical trials of interventions to mitigate the effects of cough and wheeze on SCD morbidity are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cumulative Incidence of cough or wheeze

Cumulative incidence plot depicting the amount of time that elapsed before a given participant recorded a positive response to the question “over the last 2 months has the participant had any cough or wheeze?” At study entry, 9 participants (19%) answered yes to the question. With repeated follow-up surveys, the proportion rose to 68%. Vertical marks indicate censor events (i.e., end of follow-up for that participant).