The Epidemiology and Management of Lung Diseases in Sickle Cell Disease

Lessons Learned from Acute and Chronic Lung Disease in Cystic Fibrosis

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KEYWORDS

• Sickle cell disease • Cystic fibrosis • Lung disease

KEY POINTS

- Both sickle cell disease and cystic fibrosis are common monogenic disorders with significant improvements seen in survival across the lifespan but with vast differences in collaboration and funding efforts.
- There is much to be learned by the sickle cell community from the advances made in cystic fibrosis.

INTRODUCTION

Sickle cell disease (SCD) and cystic fibrosis (CF) are two of the most common monogenic diseases presenting in childhood worldwide. SCD affects approximately 100,000 individuals in the United States and is more common in individuals of African-American descent, occurring in 1 out of every 365 black births.[1] Worldwide, estimates suggest 300,000 babies with SCD are born every year.[2] Approximately 30,000 individuals are living with CF in the United States, and 70,000 worldwide. CF is most common in individuals of European ancestry, occurring in 1 out of every 3200 white births in the United States.[3] Significant advances in medical management of CF and SCD over the past two decades have transformed what were once a near fatal childhood diseases into chronic conditions with survival into the fifth or sixth decade of life.[4,5] This success creates new challenges, as more is learned about

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how both diseases develop across the lifespan, with disease-specific manifestations that change with age.

Despite these commonalities, CF and SCD enjoy vastly different funding and collaborative research efforts.[6] Currently the CF registry has more than 20,000 registrants providing key information regarding the clinical history and comparativeness of various interventions. A similar registry has not been established for SCD, limiting the broader understanding changing disease phenotype as affected individuals age. Additionally, disease-specific funding for CF as compared with SCD from the National Institutes of Health and national foundations is approximately 3.5-fold and 440-fold higher, respectively.[6] In 2011, funding per affected individual was 11.4-fold greater for CF than SCD, and there were nearly twice as many publications in the field of CF when compared with SCD.[6] Clearly, there are likely opportunities for the SCD research community to learn from the work being done in CF.

Both SCD and CF are multisystem diseases and require multidisciplinary care. However, CF has primarily been considered a disease of the lungs, with inflammation, recurrent infections, and lung pathology known to be present as early as the first few months of life.[4] Defining, monitoring, and treating lung disease is considered central to the clinical management of CF, but in SCD pulmonary complications have been considered one of many separate morbidities. To the extent that the lung in SCD has been studied, attention has mainly focused on acute life-threatening complications, such as acute chest syndrome (ACS). The following review compares and contrasts significant knowledge about acute and chronic lung disease and optimal management in CF with the dearth of knowledge regarding acute and chronic lung disease in SCD.

ACUTE LUNG DISEASE EXACERBATIONS ARE COMMON IN BOTH SICKLE CELL DISEASE AND CYSTIC FIBROSIS

Periodic flares of lung disease in CF and SCD are associated with significant morbidity and mortality. The accepted definition of these flares is not universally accepted in either disease, making understanding of the triggers, mechanism, and pathophysiologic consequences challenging.

"Pulmonary exacerbation" describes periodic episodes of acute worsening of pulmonary status, commonly seen in CF. More than a third of individuals with CF experience at least one pulmonary exacerbation requiring intravenous antibiotics per year.[7] A universally accepted definition of what constitutes an exacerbation is not currently in use. However, symptoms include decreased exercise tolerance, increased cough, increased sputum production, abnormal respiratory examination, decreased appetite, and school or work absenteeism.[8] Severe pulmonary exacerbations have well-established long-term effects including a decline in lung function[9] and decreased 5-year survivorship.[10] A retrospective cohort study of 851 individuals with CF demonstrated that half of the decline seen in forced expiratory volume in 1 second (FEV_1) was associated with pulmonary exacerbations, and for a given number of exacerbations, the annual rate of FEV_1 decline was greatest in individuals with less than 6 months between exacerbations.[11] These associations motivated the development of clear guidelines for recommended management and targeted therapy for pulmonary exacerbations in CF.[7]

An acute flare in respiratory disease in individual with SCD is termed ACS. ACS is also a common complication with a reported rate of 12.8 hospitalizations per 100-patient years.[12] As in CF, there is no universally accepted definition of ACS. Common criteria used for research include a new infiltrate seen on chest radiograph and one of the following symptoms: cough, chest pain, fever, tachypnea, abnormal