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Review

Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment

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Abstract

Background: Studies have described illness associated with cystic fibrosis (CF) early in life, but there is no comprehensive accounting of the prevalence and ages of disease manifestation and progression described in individual studies.
Methods: We searched for peer-reviewed English-language studies of the health of children ≤6 years old with CF (published 1990–2014). Structural abnormalities and dysfunction of the digestive and respiratory systems were summarized across relevant studies by system and age group.
Results: Primary studies (125 total) from 22 countries described abnormalities, dysfunction, and disease progression in infancy and early childhood. Improved health was consistently observed in association with diagnosis via newborn screening compared with cohorts diagnosed later by symptomatic presentation.
Conclusions: The peer-reviewed literature is remarkably consistent: CF-associated growth impairment and airway abnormalities are reported at birth, and disease progression is reported in infancy and throughout childhood. Earlier access to routine CF management is associated with improved subsequent health status.

Keywords: Child; Disease progression; Comprehensive survey; Data collection; Infant; Preschool; Health status

Contents

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1. Introduction

Cystic fibrosis (CF) is a life-shortening, multisystem genetic disease. Since the 1930s, the development and use of an arsenal of symptomatic treatments and extensive prophylactic daily treatment regimens have extended the CF median predicted survival from just a few months following diagnosis to 38 years of age for the cohort in the US CF Foundation Patient Registry in the years 2008 to 2012 [1], and 34 to 44 years of age for the cohort in the United Kingdom (UK) CF Registry in the years 2009 to 2013 [2]. Despite this dramatic improvement, CF continues to be characterized by digestive and respiratory dysfunction contributing to growth deficits, chronic respiratory infection, progressive lung tissue damage, and premature death [1]. The median age of death among individuals with CF followed in the US and UK patient registries was 27 to 28 years in 2012 [1,2].

The discovery of the mutated CF gene (cystic fibrosis transmembrane conductance regulator; *CFTR*) in 1989 [3,4] and the function of wild-type CFTR protein in 1992 [5] established the underlying pathophysiology present in CF epithelial tissues, including that of the sweat gland, the pancreas, the airway, and the intestine. It is now recognized that interventions targeting the underlying *CFTR* defect across body systems have the potential to improve outcomes throughout life for persons with CF. Because CF is a progressive, multiorgan disease, initiation of symptomatic and prophylactic treatments early in life with the help of newborn screening has been shown to improve outcomes compared with later initiation of treatment secondary to later diagnosis [6]. Similarly, it is likely that the initiation of interventions that target the underlying *CFTR* defect before significant disease progression has great potential to avoid accumulation of tissue damage, allowing for better health maintenance and more normal function for persons with CF. The optimal time for initiation of treatments is dependent on when complications and cumulative damage begin to occur in persons with CF.

It has long been appreciated that newborns with CF can have serious pancreatic insufficiency and gastrointestinal complications related to their disease, as discussed in two recent reviews [7,8]. In contrast, only fairly recently reviews [9–11] and critical analyses [12,13] have begun to suggest that abnormalities of the respiratory system consistent with early disease progression can be observed early in life in children with CF. To date, a comprehensive review of the ages of earliest disease manifestation and progression across organ systems is lacking, which represents a knowledge gap. Although it is understood that disease progression will be unique to each individual, it is important to establish the ages at which CF signs and symptoms manifest and disease progression have been observed on a large scale. Thus, we undertook a comprehensive review of published primary studies of health, disease, and disease progression in the respiratory and digestive systems reported for young children with CF worldwide. We focused on the respiratory and digestive systems because the major symptoms and causes of death are associated with these two body systems [1].

The three research questions were: (1) At what ages have CF-related dysfunction and structural differences been demonstrated in young children with CF ($\leq$6 years of age)? (2) At what ages has disease progression been reported in young children with CF? (3) At what ages are there improved outcomes with early versus late treatment initiation in young children with CF?

2. Methods

2.1. Search details and dates

Three large literature databases (MEDLINE, CENTRAL, and EMBASE) were searched between June and August 2014 for peer-reviewed, English-language, primary studies of the health of young children ($\leq$6 years of age) with CF. The search strategy (Supplementary Material 1) was designed to capture a broad range of study types to provide a comprehensive summary of available results. Studies of treated and/or untreated children with CF (all genotypes) published between January 1, 1990 and August 6, 2014 were included. Studies including a wider age range were included only if outcomes for children aged 6 years or younger were analyzed separately from outcomes for older groups. Reviews, systematic reviews, meta-analyses, animal studies, studies of older persons only, non–peer-reviewed publications, case studies, and treatment or diagnosis guidelines were excluded.

Duplicate citations and articles of inappropriate types, publication dates, and language were removed in a primary sort. A secondary sorting of titles and abstracts eliminated inappropriate study populations (non-CF, adults, older children, parents) and in vitro studies. A single researcher conducted the first two sorting phases. A final sorting of titles and abstracts restricted the articles included to relevant studies of the digestive and/or respiratory systems in young children (study sample ages $\leq$6 years were determined from the title or abstract of each study). Two researchers performed the final sort independently and agreed on inclusion of each study, with discrepancies resolved upon reading the full text. Two researchers extracted data from each study independently from each other.