Foretelling Early Lung Disease Progression in Cystic Fibrosis: The Combined Benefits of Magnetic Resonance Imaging and Newborn Screening

Early disease identification leads to targeted subspecialty care and improved health outcomes. This concept underlies universal newborn screening (NBS) for cystic fibrosis (CF), which has been in place in the United States since 2010. However, NBS has not been proven to have a demonstrable effect on the progression of CF lung disease despite improvements in nutrition and growth of infants with CF (1). Although it is simple to detect changes in weight as a result of pancreatic enzyme use instituted in the first few weeks of life, it has been much more challenging to prove benefits in lung disease progression (2–4).

The availability of highly effective CFTR (CF transmembrane conductance regulator) modulators to target the root cause of the disease (5–8) offers significant hope to parents of children with CF that lung disease onset and progression can be minimized. However, the development of tools to noninvasively detect asymptomatic disease and identify the highest risk infants for earlier aggressive therapy have not advanced nearly as rapidly as these therapies. This leaves parents and clinicians in an uncertain place regarding the potential long-term risks of using novel medications in a vulnerable population versus the hope for a better future.

Spirometry is the standard outcome measure for most studies of lung function in obstructive airways disease but cannot be reliably performed in infants and preschoolers. Specialized infant lung function testing is available only in a few centers with the clinical expertise to routinely perform and interpret these tests. Multiple breath nitrogen washout is gaining traction as a promising technique to detect ventilation inhomogeneity but, as of yet, is still limited to research use.

The assessment of lung structural changes via chest radiograph has very low sensitivity and specificity (9), and although computed tomography scan has been shown to enhance the detection of airway abnormalities in young infants and children with CF (10), the associated radiation dose required for serial monitoring is considered unacceptable to many. In contrast, magnetic resonance imaging (MRI) can be serially performed without radiation, providing detailed reconstructed images for the detection of subtle airway abnormalities. Previous cross-sectional studies have shown MRI sensitively detects early lung disease in infants and preschoolers with CF (11, 12). Yet the ability of MRI to longitudinally track disease progression and characterize the impact of early diagnosis via NBS (vs. later clinical diagnosis) has not been previously shown.

In this issue of the *Journal*, Stahl and colleagues (pp. 943–953) elegantly demonstrate the progression of early lung disease in preschool children with CF in a longitudinal study using MRI (13). This group of experienced MR imaging researchers capitalized on the rollout of an NBS pilot program in Southwestern Germany in 2016. In this unique scenario, 47% percent of maternity clinics in the catchment area participated in the NBS pilot program, whereas the remaining 53% of clinics did not offer NBS to expectant parents. This latter group of children, therefore, were not diagnosed until the onset of clinical symptoms. After diagnosis, all children were followed at the same CF center and received similar standard of care treatments, thus allowing for a clear distinction of the contribution of NBS to detection and prevention of asymptomatic lung disease. The researchers further subdivided the symptomatic group into those with an early clinical diagnosis (ECD; made within the first 4 months of life) and those with a late clinical diagnosis (LCD; diagnosed after 4 months of life). MRI was obtained around the time of diagnosis (mean 2.5 months after diagnosis) in all participants and then annually in these distinct yet concurrent cohorts: NBS ($n = 28$), ECD ($n = 37$), and LCD ($n = 31$). Data obtained during clinical visits for children allowed for comparison of disease progression over a period of 4 years and established an association with respiratory symptoms, airway microbiology, and CF pulmonary exacerbations. Strikingly, MRI global scores increased significantly from baseline to age 4 in all cohorts, and the prevalence of lung disease detectable by MRI was universal by the final follow-up scan. The detected lung abnormalities were predominantly airway wall thickness and/or bronchiectasis and the presence of luminal mucus.

The importance of comparing contemporaneous groups of children held to the same clinical standard cannot be understated. All groups were started on chronic inhaled therapies at the time of diagnosis, but the LCD group was diagnosed at a mean age of 21.6 months, compared with 2.0 months for the ECD group and 1.1 months for the NBS group. Stahl and colleagues (13) were able to show for the first time that infants identified by NBS showed milder wall thickening and bronchiectasis at all time points in the study compared with those in the ECD or LCD groups. MRI-detected changes in lung morphology and perfusion also correlated with pulmonary exacerbations. Despite this, there was a similar trajectory of progression of lung disease in all participants, regardless of the age at diagnosis. The relentless progression of lung disease, even in those who were treated with chest physiotherapy and inhaled osmotic hydrators from very early in life, suggests that to fully capitalize on the potential benefits of early diagnosis by NBS, we should be moving toward more aggressive therapies, including CFTR modulators in infants.

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Not only does this study suggest the need for increased therapies targeting asymptomatic lung disease in infants and preschoolers, but it also adds to accumulating data that suggest that MRI is a viable outcome measure for future interventional studies of treatment of mild or asymptomatic lung disease. Although sedation with choral hydrate is routinely used for imaging procedures in Europe, advances are being made in MR image acquisition time (14) and distraction techniques (15) to improve imaging results in unsedated infants. The incorporation of such measures may negate the need for sedation in future studies, further expanding the appeal of MRI for very young children.

The landscape of CF therapeutics is changing rapidly, and outcome measures used to detect disease must follow suit. With this well-designed observational study of radiographic abnormalities in infants with CF detected by NBS or clinical symptoms, Stahl and colleagues (13) continue to push forward to establish lung MRI as the standard of care for the detection of mild, asymptomatic CF lung disease. ■

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The Epigenomic Landscape: A Cornerstone of Macrophage Phenotype Regulation in the Fibrotic Lung

Macrophages are immunological cells that are present throughout the lungs. Based on the location and subtype of the macrophage, they play different roles during homeostasis or in the setting of injury or repair. Macrophages, although terminally differentiated cells, have high plasticity and respond to environmental stimulus as well as their anatomical location by having different polarization phenotypes (1). The heterogeneity within the macrophage subpopulations of the lung has been highlighted in the setting of chronic lung diseases such as pulmonary fibrosis. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, nonresolving interstitial lung disease of unknown etiology that is characterized by excessive extracellular matrix deposition, leading to reduced lung compliance and disruption of gas

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