Optimising respiratory health in children with cystic fibrosis

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Abstract

Cystic fibrosis is a multi-system genetic disorder causing thick secretions, lung infection and pancreatic insufficiency. Optimising respiratory health in children with cystic fibrosis depends upon meticulous attention to maintaining general health, in addition to preserving lung health. Maximising nutrition and growth are essential as these are independent predictors of lung function and survival.

Neonatal screening has enabled an earlier, more proactive approach to optimising health. However the primary predictor of deterioration is the acquisition of the opportunistic bacterium *Pseudomonas aeruginosa*. Eradication of chronic infection with this organism is impossible, leading to lung destruction and shortened life expectancy for individuals with CF. The optimal strategies for managing this critical complication of cystic fibrosis are the subject of ongoing research, however these strategies may depend upon antibiotic regimens to which the bacteria may gain resistance. Novel strategies, adopted alongside continued improvements in care, are needed to further defer the complications and deterioration experienced by patients with cystic fibrosis, enhance quality of life and extend survival.

Keywords cystic fibrosis; infection; pseudomonas

Introduction

Cystic fibrosis (CF) is a multi-organ disease with recurrent and chronic lung infection being the critical life-limiting feature. The subsequent lung destruction, accompanied by pancreatic insufficiency, alongside increased metabolic demands, adversely affects growth and leads to respiratory failure, a reduced quality of life and premature death. In infants, treatment focuses on early aggressive management of lung infection and optimisation of nutritional status. This continues alongside treatment of complications in later childhood.

Cystic Fibrosis is the commonest life-limiting autosomal recessive condition, in the UK approximately 10,000 people have manifest disease. Forty years ago, few children survived beyond infancy however improvements in management have led to dramatic changes in the life expectancy for patients with CF. The mean life expectancy for a baby born in 2003 was 42 years for a boy and 36 years for a girl. The aim of current research and clinical care is to increase this to beyond 50 years. Traditionally the survival for girls with CF appeared to be worse than that of their male counterparts, however this may not necessarily be universal.

There are numerous gene mutations that effect a change in the presence or function of the cystic fibrosis transmembrane regulator (CFTR). This cell membrane protein acts directly as a chloride channel but is also responsible for regulating the epithelial sodium channel (ENaC). The net result being impaired chloride transport and excess sodium loss resulting in a depletion of the airway surface liquid and thick mucus, entrapping cell surface cilia. CFTR mutations also may be responsible for facilitating infection with early non-mucoid *Pseudomonas aeruginosa* and reducing the efficacy of the adaptive immune response to later mucoid *P. aeruginosa*.

The effects upon the function of CFTR are not restricted to the lungs, resulting in the complications of pancreatic exocrine and eventual endocrine insufficiency, abnormal intestinal function and poor nutrition, skin salt loss, metabolic abnormalities and biliary fibrosis. Nasal polyps, congenital absence of the vas deferens and CF related arthritis further add to the effect the disease has on quality of life.

Inflammation and infection

Those with cystic fibrosis have an up-regulated inflammatory cascade, however it has been contentious whether this is due to an intrinsic pro-inflammatory state, disproportionate inflammation in result to infection or a proportionate immune response. In studies aimed at answering this question extensive examination of Bronchoalveolar lavage (BAL) fluid suggests that those with infection have significantly increased levels of inflammatory mediators compared to those without.

Attempts at ameliorating the lung damage with oral corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated improvements in lung function. Concerns regarding side effects have however, prevented the long term use of oral corticosteroids.

Early care

Age at diagnosis is significantly associated with survival such that for each year increase in age at diagnosis significantly increases the acquisition of *P. aeruginosa* and reduces lung function and survival.

Diagnosis

The diagnosis of cystic fibrosis depends upon the presence of one or more characteristic phenotypic features, a positive newborn screening test result or a history of CF in a sibling and laboratory evidence of a CFTR abnormality. CFTR abnormality may be demonstrated by elevated sweat chloride concentration, identification of mutations in each CFTR gene known to cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium. In the UK however since

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the introduction of universal neonatal screening, the vast majority of diagnoses are made via this route.

The justification for neonatal screening revolves around recent improvements in outcome that have been attributed to improvements in intervention. The natural suggestion is that if these improvements are instituted earlier, before lung damage and nutritional status is impaired, that clinical status will improve. There are obvious confounders in outcomes of screening, an intervention that was instituted at the same time as other improvements in management. However US CF Registry data strongly suggest that screening confers a survival advantage.

Superficially, the early clinical course of children with CF can be split — those diagnosed through screening and those diagnosed prior to the neonatal screening procedure due to an early complication. This group of patients largely present due to meconium ileus.

The effect of meconium ileus

The influence that meconium ileus has on outcomes for children with CF has been controversial. A large study including the 27 703 patients on the Cystic Fibrosis registry between 1986 and 2000 (including the pre-screening era) concluded that the risk of acquiring *P. aeruginosa* and mortality was significantly higher in those who presented with meconium ileus compared to those identified through screening. In the pre-screening era it is possible that the disadvantage conferred by having meconium ileus was reduced by the advantage of earlier diagnosis such that there were no differences in lung function, weight and height and acquisition of *P. aeruginosa* in those early studies. Now we have entered the screening era this 'advantage' may have disappeared. An Australian head-to-head comparison with 39 children in each group of those diagnosed through screening or through presentation with meconium ileus demonstrated that whilst having meconium ileus appeared not to affect nutritional status, or predispose to other complications of CF, lung function and Schwachman scores were significantly worse in those who had presented with meconium ileus.

CFTR potentiation, correction and gene therapy

In 2015 the results of the Gene Therapy Consortium's placebo controlled double blind randomised controlled trial of liposomal delivery of wild-type CFTR will be available. This is the first multiple dosing trial in a planned development programme that could include viral delivery mechanisms. If successful, and delivered sufficiently early prior to lung damage, the natural history of CF may change considerably. However, even if this first trial demonstrates significant benefit, the development process is likely to consist of incremental improvements that will be some time before this therapy is available to children with CF.

CFTR potentiation on the other hand, is delivering measurable benefit to a small subset of patients with CF. Ivacaftor (Kalydeco), a small molecule that potentiates the action of CFTR in those with gating mutations (in particular G551D). Available to those over 6 years old, through a twice daily tablet, effects of Ivacaftor include normalisation of sweat chloride, improvement in lung function, body mass index (BMI) and pulmonary exacerbation rate.

At the end of 2014 the results will be available for clinical trials (TRAFFIC and TRANSPORT) assessing the combination of Ivacaftor with Lumacaftor (a CFTR corrector) in those homozygous with dF508 mutation.

The remaining questions regarding providing CFTR correction and potentiation concern how early it is possible to administer these drugs to young children. Indeed it is conceivable that those receiving these medications from birth will experience the greatest benefits. However access to these transformational medicines is accompanied by economic and ethical considerations with each year of Ivacaftor treatment costing £182 500 per patient (BNFc).

Lung infection

Whilst accounting for the effect of age of diagnosis upon outcome, acquisition of *P. aeruginosa* is independently responsible for deterioration. It is therefore a priority to aim to defer and even eradicate lung infection in those with CF.

Identification of infection

Identification of infection so that treatment may be given for lung infection is therefore crucial. Respiratory cultures are recommended at each medical contact. However, as infants cannot expectorate, microbiological evidence of infection depends on oropharyngeal (OP) cultures which, whilst having good specificity (95%), have poor sensitivity (44%) resulting in antibiotics being withheld in circumstances where a positive culture would be accompanied by the prescription of antibiotics. The presence of symptoms is also a poor predictor of lung infection as up to 20% of asymptomatic infants have pathogens identified at BAL.

Currently most patients have treatment guided by regular OP cultures. With evidence that in children younger than 6 years BAL is well tolerated, with only 3% of procedures being associated with a clinically significant adverse effect related to the procedure, it is likely that in future BAL will become a more common undertaking and treatment, as a result, will become more targeted.

Infections of the CF lung

The altered lung environment in those with CF provides an ideal niche for bacterial growth. There appears to be a recognisable sequence of escalation in the organisms isolated from children with CF (Figure 1). One can speculate that this progression represents a change in competitive advantage between species.

In infancy *Staphylococcus aureus* predominates as the most common organism isolated (50%) with the prevalence peaking in the 6—10 age group. *Haemophilus influenzae* and *P. aeruginosa* are similarly prevalent until about age 5 (30—35% prevalence) when the prevalence of *P. aeruginosa* increases such that it is the most common organism isolated in the 11—17 age group with a prevalence increasing to 37.8% in the late-teens.

The opportunist *P. aeruginosa* eventually establishes a chronic infection causing reduced growth, faster deterioration of lung function and progression to end-stage lung disease as evidenced by lung transplantation or death. Decline in lung function is largely responsible for the morbidity and mortality in CF and over the last two decades more efficient treatment of pulmonary