Origins of growth deficiencies in cystic fibrosis

Trang N Le,[1] Michael S Schechter[2]

The majority of individuals with cystic fibrosis (CF), primarily those with CF transmembrane regulator (CFTR) class I, II or III mutations, have pancreatic insufficiency and protein/fat malabsorption requiring nutritional management and pancreatic enzyme replacement therapy.[1] While the focus of CF treatment over the last 50 years has been on lung disease, the relationship between nutrition (as reflected by weight) and life expectancy in people with CF has long been appreciated. Infants who achieve a weight z-score at 2 years of age that is at or above their birth weight z-score have significantly better lung function at age 6,[2] and low weight for age and weight for length during early childhood is a risk factor for early mortality.[3 4] Implementation of CF newborn screening, along with high-calorie nutrition interventions and pancreatic enzyme replacement, has led to significantly improved growth parameters in children with CF over the last few decades.[5 6]

Malabsorption, in combination with increased metabolic expenditures related to lung disease, is the most obvious cause of poor growth in CF. Nutritional interventions have been able to achieve a relative normalisation of weight but have been less successful at preventing or reversing stunting. Only 32% of children diagnosed by newborn screening in the Wisconsin Randomized Clinical Trial achieved target mid-parental height by puberty[7]; in 2012, the year of that analysis, 54% of children 2–19 years of age in the CF Foundation national registry were above the 50th percentile for body mass index.[8] Infants participating in the Baby Observational and Nutritional Study showed an increase in their weight z-score, but a decrease in length z-score during their first year of life, and nearly twice as many (24%) were below the 10th percentile for length than were below the 10th percentile for weight (24%). It appears that there are growth abnormalities in children with CF that are not reversed by treatment of malabsorption.

Schlüter and colleagues have evaluated the influence of CF on birth weight by analysing data from two large population-based cohorts from Wales and Denmark.[9] Average birth weight was approximately 200 g lower in those born with CF when compared with unaffected neonates, with only 40% of this difference in birth weight explained by earlier gestational age. Babies with CF had a higher risk of low birth weight than unaffected babies, with the estimated probability ranging from 1.3 to 1.8 to 1.2–2.1 times higher Welsh and Danish databases, respectively.

The results of Schlüter *et al*'s study confirm previous findings of low birth weight in CF neonates.[6 10–13] In a study comparing Italian newborns with and without CF, birth weight was not significantly different in infants born prematurely, but among those born at 37 weeks' gestational age or later, CF infants were approximately 205 g smaller[12]; this weight divergence beginning later in gestation has also been confirmed in a CF mouse model.[14] There are limited data available on intrauterine growth in CF, but effects on birth length have also been noted.[6 13] This difference cannot be attributed, obviously, to prenatal pancreatic malabsorption or lung disease. Inflammation and tissue destruction in utero, as seen in neonatal CF pigs with evidence of variable degrees of inflammation pancreas, liver and intestinal sites of perforation and necrosis,[15] may contribute to increased metabolic requirements and divert energy away from growth. Impaired fetal pancreatic exocrine function and abnormal maternal-fetal placental function for nutrient and fluid transfer have been proposed as contributors to lower birth weight in CF,[11] but data to support these hypotheses remain limited.

CFTR is expressed in the placenta[16]; in vitro inhibition of CFTR function is associated with lower expression of placental aquaporins important for maternal-fetal transfer of fluids and solutes.[17] However, lower aquaporin expression in CF mice as compared with control mice did not correlate with decreased fluid exchange,[14] leaving the contribution of placental CFTR derangements to intrauterine growth unresolved. Intestinal obstruction and meconium ileus may be seen in neonates with CF. Studies of congenital intestinal obstruction in non-CF infants that have shown reduced birth weight[18 19] have proposed that reduction of enteral amniotic fluid uptake may result in reduction of fetal delivery of growth factors and nutrients; this potential mechanism of poor intrauterine growth has not been studied in CF.

The growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis is the primary driver of linear growth in children; GH is secreted by the anterior pituitary and acts to increase IGF-1 production in several target tissues, such as the growth plates of the long bones, to effect linear growth. The GH-IGF-1 axis is suppressed in states of malnutrition and in chronic illness or inflammation, resulting in the growth stunting that is commonly seen in chronic diseases of childhood.[20] IGF-1 has previously been found to be decreased in children and adults with CF[21 22] and is attributed to CF-related malnutrition and inflammation. However, IGF-1 has also been found to be already lower at birth in neonates and infants with CF,[6 23] raising the possibility of a direct role for CFTR in modulating the growth impairment beginning during gestation.

There are animal and human data to support this hypothesis. At birth, CFTR/ΔF508 pigs already manifest lower IGF-1 levels, decreased humerus length and lower bone mineral content than their littermate controls; weight was also lower but did not reach statistical significance.[23] The magnitude of GH release by pituitary cell cultures of newborn CFTR/ΔF508 pigs is lower than in control pigs,[23] suggesting that defects in CFTR may influence the GH-IGF-1 axis at the level of the pituitary in addition to the effects at end organs such as long bone growth plates.

In CF mice and also in a *Cftr*$^{inv/fl10}$+villin-Cre mice (a model with correctable intestinal obstruction), adult CF mice had lower IGF-1 compared with wild-type littermates; these lower IGF-1 levels were correlated with decreased weight and length.[14] Of note, there were no differences in IGF-1 levels in late gestation or at birth; levels of CF mice did not diverge from control mice until 3 weeks' postnatal age.[14] Thus, while reductions in IGF-1 in CF are observed among humans, pigs and mice, the timing of these changes is not necessarily consistent between humans and various animal models. In a rat CF knockout model, femur length and growth

[1]Internal Medicine and Pediatrics, Virginia Commonwealth University, Richmond, Virginia, USA
[2]Pediatrics, Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence to Dr Michael S Schechter, Pediatrics, Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, VA 23298, USA; michael.schechter@vcuhealth.org

plate thickness were reduced in both *Cftr*-/- male and female rats compared with wild type, which was accompanied by severe reductions in serum IGF-I concentrations.[24]

The relationship between CF and the GH-IGF-1 axis is likely more complex than can be appreciated from the above models. Trials of recombinant human GH treatment in CF have shown improvements in height and weight, but the number of studies and subjects remains small.[25] A single study (n=7) of prepubertal children with CF treated for 6 months with recombinant human IGF-1 did not show any effect on linear growth or weight gain. As CFTR is expressed in human bone cells, including the osteocytes (osteoblasts and osteoclasts)[26] found in the growth plates of long bones, there may be direct effects of CFTR mutations on the normal growth plate response to IGF-1. Given the finding of lower IGF-1 levels in CF, CFTR mutations could therefore have separate and potentially additive effects at the growth plate.

If there is a direct influence of CFTR on growth, it follows that correction of defective CFTR synthesis, transport or functionality would result in improved growth parameters. To this end, a post hoc analysis of weight and linear growth was conducted among prepubertal subjects (n=83) with CF and at least one G551D-CFTR mutation, who were enrolled in two studies involving the CFTR potentiator ivacaftor.[27] Significant improvements in height and weight z-scores were accompanied by improvements in growth velocity by 6 months, and remained higher than placebo through 48 weeks of follow-up.[27]

Several areas are thus worthy of future study regarding the multifactorial origins of suboptimal growth in CF. Meticulous collection of birth weight and length in registry data will allow for improved monitoring in shifts in growth trends over time as standards of care in CF continue to evolve. Unfortunately, the databases used in the analysis by Schlüter *et al* contained no data on birth length; a better understanding of the prenatal relationship between weight and length would be of great interest. The finding of intrauterine growth alterations suggests potential new therapeutic targets. A single-centre study from Cleveland found a correlation between birth weight and FEV1 at ages 6 and 10 years,[10] suggesting that interventions to reverse prenatal CF-related growth deficiencies might be of long-term benefit. The introduction of new CFTR modulator therapies to younger age groups, and eventually to pregnant women with affected fetuses, presents opportunities for personalised care affecting not just lung disease but CF growth outcomes as well.

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