NUTRITIONAL STATUS AND GROWTH IN INFANTS WITH CYSTIC FIBROSIS
AT DIAGNOSIS AND AT AGE TWO YEARS AND SIX YEARS

by

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ABSTRACT

Nutritional Status and Growth in Infants with Cystic Fibrosis at Diagnosis and at Age Two Years and Six Years

by

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PURPOSE: A retrospective chart review was conducted to determine if nutritional source of feeding and/or infant age at diagnosis of cystic fibrosis had any effect on nutritional status and subsequent growth accretion. Additionally, an attempt was made to identify predictors for poor growth in patients with undiagnosed cystic fibrosis.

METHODS: Data was collected from medical and clinic charts at Primary Children’s Medical Center (PCMC), Salt Lake City, Utah, for subjects born between January 1, 1995 and December 31, 2001, who were diagnosed with cystic fibrosis before 1 year of age. Thirty-one subjects met inclusion parameters. These subjects were divided into two groups: an “early” diagnosis group (N=13) included those who were diagnosed before 9 weeks of age, and a “late” diagnosis group (N=18) included those who were diagnosed after 9 weeks of age. “Breastfed at diagnosis” (N=7) and “not breastfed at diagnosis” (N=17) groups were established as well, with nutritional source of feeding remaining
unknown for 7 of the 31 subjects. RESULTS: Paired t-tests indicated that children who were primarily breastfed at time of diagnosis did not grow significantly more than children who were formula-fed at time of diagnosis, although regression analysis indicated that nutritional source of feeding at time of diagnosis was a significant predictor of growth later in life. This contradiction could have come about due to the small sample size. Age at diagnosis had a significant effect on growth, at diagnosis, at age 2 years, and age 6 years. Children who were diagnosed early grew taller and weighed more than the children who were diagnosed after 9 weeks of age, both at the 2-year mark and at the 6-year mark. Additionally, low blood albumin levels at diagnosis were predictive of more growth at age 2 years and 6 years. Other identified predictors of growth included gender, age at diagnosis, and whether the child had a family history of cystic fibrosis. This research highlights the crucial need for early detection and correction of malnutrition in infants and children with cystic fibrosis. It should be viewed as a pilot study, with more research needed in this area.
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CHAPTER I
GENERAL INTRODUCTION

DEFINITION OF CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disorder that affects the exocrine glands of the lungs, gastrointestinal tract and sweat glands (1,2). It is the most common genetic disease among Caucasian populations; incidence has been reported to be anywhere from 1:2,900 to 1:4,000 in white populations and 1:10,000 to 1:17,000 in non-white populations (1-4). Females tend to have poorer prognoses and shorter survival times than males (5).

CF is caused by a genetic mutation on chromosome 7 which expresses the cystic fibrosis transmembrane regulatory protein (CFTR). This protein regulates ion transport, especially chloride, in epithelial cells of the pancreatic ducts, sweat glands and lungs (3). The most common mutation occurs when 3 base pairs are deleted at codon 508; this is known as the ΔF508 mutation, and has been estimated to comprise about 76% of all CF mutations (6). Even though ΔF508 is the most common mutation, there are over 150 other mutations that can cause CF (3,6).

It is common for diagnosis of CF to be delayed when newborn screening is not done, and death can occur before diagnosis is made (1,3). Often, the disease is mistaken for other conditions such as asthma, allergies, bronchitis or malabsorptive syndromes of the intestinal tract (7). The average age of diagnosis is 6 months, with 70% of patients diagnosed by 1 year of age (8,9). Milder forms of the disease are often diagnosed later in life. The majority of children are diagnosed before the age of 3 years due to the development of failure to thrive, severe respiratory or gastrointestinal complications.
These extreme complications are interrelated, and early diagnosis and treatment may help alleviate or prevent them by interrupting the cascade of adverse effects that is induced and exacerbated by CF-related malnutrition.

PANCREATIC INSUFFICIENCY AND MALABSORPTION

Pancreatic insufficiency (PI) is the state of having an inadequate amount of digestive enzymes available in the gastrointestinal tract, and is common in children diagnosed with CF. The production of trypsin and lipases are the most severely affected, which seriously hampers the digestion and absorption of protein and fat (10). This problem is corrected with the ingestion of the proper replacement enzymes.

The extent of nutrient malabsorption seen in CF is tied to the severity of PI (10). This, in turn, can lead to malnutrition and poor growth in affected children. Other causes of poor growth could include anorexia resulting from chronic salt depletion (11) or increased resting energy requirements for children with CF (12).

It has been estimated that about two-thirds of infants diagnosed with CF have PI at diagnosis (13). PI is associated with more severe CF; certain genotypes, such as homozygous ΔF508 mutation, are predictive of worse pancreatic status (6,14,15). PI can also develop over time, with milder cases of CF-related malabsorption becoming more severe as the patient ages.

An early study of growth patterns in CF patients revealed that these children tend to be significantly smaller than their normal cohorts (16). This effect was particularly pronounced just prior to the growth spurt typically seen in children without CF, and there
was a significant relationship between pulmonary disease and stunted growth. As may be expected, greater degrees of PI lead to more severely compromised nutritional states, but the study indicated no significant correlation between degree of PI and stunting. This was possibly due to the corrective effect of proper enzyme therapy, since the best growth is seen in patients with CF who are taking the correct dosage of enzymes (6,16).

Fat malabsorption seen in CF can create deficiencies of essential fatty acids (EFA) in CF patients. EFA are incorporated into cell membranes and appear to be related to proper functioning of the CFTR protein (17). Patients with CF have lower blood levels of EFA, including gamma linoleic acid, alpha linoleic acid, docosapentaenoic acid and polyunsaturated fatty acids (10,17-20). These lower levels of EFA are associated with greater incidences of respiratory tract infections, especially *Staphylococcus aureus* and *Pseudomonas aeruginosa* (17). Fat malabsorption seen in CF may result in EFA deficiency, leading to higher-than-normal rates of pulmonary infections. With early nutritional support, these deficiencies are correctable by age 12 months (18,21).

Decreased fat absorption also affects the absorption of fat-soluble vitamins. Low blood levels of fat-soluble vitamins, especially vitamin E and vitamin A have been seen in newly-diagnosed patients with CF, even when diagnosis is made early through screening. Vitamin D deficiencies have also been observed (15,18,22,23), and therefore routine supplementation with fat-soluble vitamins is recommended for patients with CF (14,24).
MALNUTRITION IN CYSTIC FIBROSIS

Malnutrition and decreased body mass are markers of poor prognosis for patients with CF, especially those with lung disease. It has been theorized that muscle wasting seen in malnutrition affects the muscles of the respiratory system as well as other body muscles (25-27). Additionally, malnutrition can decrease the energy supply to these muscles, resulting in respiratory fatigue. Severe lung complications place the patient with CF at higher risk for nutritional deficiencies due to difficulty consuming adequate food (14), which can perpetuate a downward spiral.

Malnutrition in infancy leads to measurable deficiencies in height and weight for height when examined years later (10). If intensive nutritional intervention is implemented, these parameters can be improved, but not completely corrected (28). Catch-up growth after severe malnutrition is difficult, if not impossible, but early screening can prevent stunting due to undiagnosed CF (4). Infants with CF diagnosed at a mean age of 5.4 weeks through a neonatal screening program remained smaller than average for weight and height and had reduced body fat stores at 1 year of age (29). This suggests that stunting may not be preventable for some infants despite early diagnosis. In addition to stunting, a decreased weight for height is also associated with increased risk for mortality, especially in patients older than 18 years of age (30).

Undernutrition is a serious issue which can result in a myriad of problems for young children with and without CF. Growth failure, increased morbidity and mortality, and delayed development have all been noted in malnourished children. Some
connections to cognitive and intellectual impairment have been noted as well, with severely malnourished children lagging behind their adequately-nourished peers (31).

Malnutrition early in life can decrease nerve growth and brain development (3,32). In one study, myelination of sciatic and optic nerves was impaired in malnourished rats. Also, there were fewer lamellae per sheath in the sciatic nerve, and the packing of nerves in their sheaths was impaired (33). Kwashiorkor and marasmus also cause significant slowing of nerve signal conductions (34). Nutrition during the first 2 years of life is critical in brain neuron development, as malnourished subjects have shorter dendrites with fewer dendritical spines compared to well-nourished subjects; this damage is considered irreversible (35).

An early study (36) noted that severe malnutrition in the first year of life decreases the number of cells in the cerebrum, cerebellum and brain stem of children (areas that normally divide most rapidly). Total brain weight in malnourished children is also reduced by 10% to 30%, and their IQs remain low even after several years (32). These effects are less pronounced if the malnutrition occurs later in life (36). CT scans of severely malnourished Nigerian children revealed that children with marasmus and/or kwashiorkor had significantly smaller brain areas than normally-nourished children (37). A recent study (38) found that children with CF who were malnourished at diagnosis had significantly lower scores on tests of cognitive functioning than those who were not malnourished.
PULMONARY FUNCTION AND HEALTH EFFECTS

Inefficient pulmonary function might affect growth in children with CF, and there are several theories to explain how this might happen. One theory is that decreased breathing results in lower tissue oxygenation and/or respiratory-related acidosis, which can impair growth (16). A second theory is that the increased work of breathing for children with significant lung disease and decreased respiratory status could also create greater caloric needs in these children (12,16). Weight gain normalizes as soon as corrective therapies are started, and is greatest when therapy is begun early in infancy. Height, however, does not normalize with corrective therapy (16).

Patients with CF who are underweight relative to their healthy cohorts have a poor prognosis (39,40). This underweight state has been significantly associated with more severe lung complications and higher mortality rates (39). Malnutrition in patients with CF prior to diagnosis has also been associated with increased severity of lung disease and respiratory complications, even when the malnutrition was corrected quickly (41). The same study shows that correction of malnutrition and improvement of growth does not necessarily translate into improvements in lung function. The nutrient deficiencies associated with malnutrition are also associated with poor immune function and increased risk of respiratory infections in children with CF.

Malnutrition has significant consequences on the lungs, including structural changes, lowered defense mechanisms and reduced muscle contractions. This could be due to inadequate dietary protein, resulting in depleted structural and blood-borne proteins, immunoglobulins and macrophages. Reduced muscle contraction creates
difficulties in breathing, which results in poor tissue oxygenation. Although blood protein levels in children with CF can be corrected with proper nutrition, the changes in lung structure can not be completely reversed (42). Gastroesophageal reflux has also been implicated in poor lung function in patients with CF, due to aspiration and reflexive spasms of lung muscles during episodes of reflux (43).

HYPOPROTEINEMIA AND HYPOALBUMINEMIA

It is suggested that infants with PI have inadequate protein intake and/or absorption. An association between undiagnosed CF and hypoproteinemia with or without edema in infants has been observed (44-48). Hypoproteinemia can include low albumin (hypoalbuminemia) and/or anemia with low hematocrit levels, and can be caused by a number of things, including inadequate dietary protein intake. It has been noted that breastfed infants tend to develop hypoalbuminemia more often than formula-fed infants in children with CF, but low albumin levels are common among all patients with CF at diagnosis and do not appear to be predictive of a worse clinical course over the long term (47). These low levels of blood proteins are associated with both breast-feeding and feeding of soy-based formula for children with CF.

Human milk has a relatively low protein content, and this could be the cause of the hypoproteinemia. However, this does not explain the hypoproteinemia seen in infants fed a soy-based formula in an earlier study (45). It is possible that, while the soy formula has more protein than human milk, the protein in the soy formula is less readily digested and absorbed (10). In spite of this, breast-fed and formula-fed infants with CF can achieve
similar growth rates and blood protein levels, apparently without the use of a protein supplement for the breastfed infants, when proper dosage of enzymes is achieved (49).

The American Academy of Pediatrics states that “[h]uman milk is uniquely superior for infant feeding....the breastfed infant is the reference or normative model against which all alternative feeding methods must be measured....breastfeeding [is] the ideal method of feeding” (50). Indeed, breastmilk with adequate pancreatic enzyme replacement appears to be adequate for infants with CF (51). Breastfeeding is not contraindicated in CF, but a protein supplement has been recommended by some sources if CF is present (46,47).

EFFECTS OF SCREENING ON EARLY DIAGNOSIS

Early diagnosis may mean early intervention for lung infections; if infections can be detected and cured quickly, irreversible damage may be delayed or prevented (52,53). A longitudinal study with a 17-year follow-up period found that newborn screening was associated with a longer life-span and healthier lungs for children with CF into young adulthood (52). Another study found that significantly more screened patients than non-screened patients survived into late childhood (53). In a 7-year study, early treatment was associated with better chest x-rays and fewer hospitalizations (54). Researchers could not determine whether the progression of lung disease was delayed, or whether close follow-up allowed for quicker treatment of lung complications (54).

Screening can also provide benefits in the areas of height and weight (15). Patients with CF who are diagnosed through screening tend to weigh more and be taller
than their non-screened cohorts with CF and to have larger OFC measurements (15,55). This difference is especially evident in the group of children with CF who also have PI. These benefits continue into childhood, with early-diagnosed patients retaining their advantage in height and weight over their late-diagnosed cohorts (15). Lung function also tends to be better in the screened group (55). Infants diagnosed before symptoms develop and treated preventatively have the best prognosis (5), although some research has found no difference in height and/or weight between early- and late-diagnosis groups (56).

Screening and early diagnosis can provide a “healthier start” for infants with cystic fibrosis (3,53). In general, newborn screenings are only used to identify possible problems and are not used to diagnose disease (3). One exception to this is the newborn genetic screening used to identify CF.

Newborn screening for CF was suggested 30 years ago, and several methods have been employed over the years in an attempt to determine the best screening method. Testing the meconium for albumin was done initially, but proved to be ineffective (3). In 1979, a method was developed that measures immunoreactive trypsinogen (IRT) levels in dried blood samples. A first sample is taken in the first few days of life, and if IRT levels are elevated a second sample is taken at 6-8 weeks of life. If that sample is also elevated, a sweat chloride test is performed to determine if cystic fibrosis is present.

This method is used alone or in combination with genetic screening for the ΔF508 mutation, and in spite of a decline in IRT levels as patients age, it is currently considered the “gold standard” for screening (3). Faster and more sensitive results can be achieved with combination testing, rather than waiting 6-8 weeks for a repeat IRT test. Screening,
especially utilizing this combination method, is extremely effective in identifying infants with CF, and has been done since 1991 (3). Early screening allows for pre-symptomatic detection of CF, thereby avoiding complications and death (3,57).

PURPOSE

There is a high incidence of malnutrition, as evidenced by low serum albumin levels, in infants with undiagnosed cystic fibrosis. It is hypothesized that exclusive breastfeeding of children with cystic fibrosis prior to diagnosis results in increased incidence of malnutrition at diagnosis and continued suboptimal growth. It is also hypothesized that “late” diagnosis (> 9 weeks of age) of children with cystic fibrosis results in increased incidence of malnutrition at diagnosis and continued suboptimal growth. This research aims to define nutritional status and growth in children with CF at the time of diagnosis and in later years, and to determine relationships between feeding and growth. The purpose of this research was four-fold:

1) To determine the nutritional status of infants with cystic fibrosis at time of diagnosis, and to compare breastfed infants with formula-fed infants to determine if one group is more susceptible to malnutrition than the other.

2) To determine growth accretion of infants and children with cystic fibrosis (in breastfed versus formula-fed infants) both prior to and after diagnosis.

3) To determine if age at diagnosis has any impact on nutritional status and/or growth accretion of infants and children with cystic fibrosis.
4) To develop a set of predictors for poor growth in patients with undiagnosed cystic fibrosis.

References


CHAPTER II

GROWTH AND NUTRITION AT DIAGNOSIS AND AT TWO YEARS OF AGE

ABSTRACT

Purpose: A retrospective chart review was conducted to determine if age and/or nutritional source (breastmilk vs. formula) of feeding at diagnosis significantly impacted growth or nutritional status of infants and children with cystic fibrosis at diagnosis and at age two years.

Methods: Charts were reviewed for nutritional and growth parameters for subjects with cystic fibrosis who were diagnosed between January 1, 1995, and December 31, 2001 and were 1 year of age or younger at time of diagnosis. Nutritional parameters included serum albumin, hematocrit, sodium, chloride, potassium, and fat-soluble vitamins A, D, and E. Growth parameters included height and weight (raw data, percentiles, and z-scores).

Paired t-tests were used to evaluate differences between groups at the time of diagnosis and at age 2 years. Regression was used to determine predictors of growth at age 2 years.

Results: Paired t-test comparisons between the breastfed group (N=7) and the formula-fed group (N=17) indicated that breastfed children and formula-fed children were not significantly different in weight or height at diagnosis or at age 2 years, although regression analysis indicated that nutritional source of feeding was a predictor for weight at age 2 years. This contradiction could have occurred because of the small sample size. Average weight and height at diagnosis differed significantly between early-diagnosis
(N=13) and late-diagnosis (N=18) groups, as did incidence of low albumin and/or hematocrit. Early-diagnosed children were still significantly taller at age 2 years. Regression analysis also indicated that low albumin was a positive growth predictor for most growth variables, and that family history of CF also predicted weight at 2 years.

INTRODUCTION

Cystic fibrosis (CF) is an inherited disorder that affects the exocrine glands of the lungs, gastrointestinal tract and sweat glands. A genetic mutation occurs in a protein that regulates ion transport, especially chloride, in epithelial cells of the pancreatic ducts, sweat glands and lungs (1). Screening and diagnosis of the disease can be done in several ways, including performance of a sweat chloride test (2). The average age of diagnosis is 6 months, and milder forms of the disease are often diagnosed later in life. The majority of children with CF are diagnosed before the age of 3 years due to the development of failure to thrive, severe respiratory complications, and/or severe gastrointestinal complications (1-3). Early diagnosis and treatment may help alleviate or prevent these problems.

Many patients with CF have pancreatic insufficiency (PI). These patients have an inadequate amount of digestive enzymes available in the gastrointestinal tract, especially trypsin and lipases. This seriously hampers the proper digestion and absorption of protein and fat, which can lead to malnutrition and poor growth in untreated children due to lack of essential "building blocks" for development and health (4). Malnutrition and decreased body mass are indicators of poor prognosis for patients, especially those with lung
disease. Treatment for PI consists of by-mouth supplementation of the missing pancreatic enzymes to help normalize digestion and absorption of protein and fat.

It is suggested that infants with PI have inadequate protein intake and/or absorption. An association between undiagnosed CF and hypoproteinemia with or without edema in infants has been observed (5-7). Hypoproteinemia can include low albumin and/or anemia with low hematocrit levels, and can be caused by a number of things, including inadequate dietary protein intake. It has been noted that breastfed infants tend to develop hypalbuminemia more often than formula-fed infants in children with CF, but low albumin levels are common among all patients with CF at diagnosis and do not appear to be predictive of a worse clinical course over the long term (6). These low levels of blood proteins are associated with both breast-feeding and feeding of soy-based formula for children with CF.

Human milk has a relatively low protein content, and this could be the cause of the hypoproteinemia. However, this does not explain the hypoproteinemia seen in infants fed a soy-based formula in an earlier study (7). It is possible that, while the soy formula has more protein than human milk, the protein in the soy formula is less readily digested and absorbed (4). In spite of this, breast-fed and formula-fed infants with CF can achieve similar growth rates and blood protein levels, apparently without the use of a protein supplement for the breastfed infants, when proper dosage of enzymes is achieved (8).

Newborn screening appears to help alleviate malnutrition and poor growth problems in children with CF. It has been noted that patients with CF who are diagnosed early through screening tend to weigh more and be taller than their non-screened CF
cohorts (9,10). This difference is especially evident in the group of CF patients with severe PI, as the early initiation of enzyme therapy leads to better growth in the early stages. These differences continue into childhood, with early-diagnosed patients retaining their advantage in height and weight over their late-diagnosed cohorts (9). Infants diagnosed before symptoms developed and treated preventatively have the best prognosis (11), but some research has found no difference in height and/or weight between early- and late-diagnosis groups (12).

The purpose of this study was to define nutritional and growth status of infants with CF at the time of diagnosis and at the age of 2 years in Utah, where prenatal screening for CF is not conducted. The aim of this study was to determine if diagnosis of CF after 2 months of age negatively affects an infant’s nutritional status and/or growth either prior to diagnosis or at 2 years of age. Additional focus of the study was to determine if exclusive breastfeeding of infants with undiagnosed CF would have the same negative impact on a child’s growth and/or nutritional status.

MATERIALS AND METHODS

Subjects were chosen from patients at the Cystic Fibrosis Clinic at Primary Children’s Medical Center (PCMC), in Salt Lake City, Utah. To be included in the study, a subject must have been born between January 1, 1995, and December 31, 2001, and must have been 52 weeks of age or younger at time of diagnosis. Date of diagnosis was determined to be either the date of the patient’s definitive positive sweat chloride test or
(in the absence of a definitive sweat chloride test) the date of the child’s initial evaluation at the Cystic Fibrosis Clinic. See Table 6 for a summary of information for each subject.

No direct intervention was planned, and no person-to-person contact with the patients occurred. The information from the records was collected by clinic workers using a standardized form and completely blinded before being given to the researcher. All identifying information and markers were removed. There was no way to identify the patients from the information given to the researcher. Patient information was protected by keeping the data forms in a locked filing cabinet in the researcher’s office.

Data were collected for nutritional and growth parameters at the time of diagnosis and for the appointment closest to the subject’s 2-year (104 week) birthday. Actual diagnosis frequently occurred 1 to 2 weeks before the initial checkup, but the parameters outlined above were not measured until the initial checkup. Therefore, the nutritional and growth measurements from the first checkup were used as the “diagnosis” measurements.

To examine the effect of age at diagnosis on growth and nutritional parameters, the data were divided into early- and late-diagnosis groups, with the early-diagnosis group including those subjects who were diagnosed before 9 weeks of age, and the late-diagnosis group including those subjects who were diagnosed after 9 weeks of age. There were 13 subjects in the early-diagnosis group, and 18 subjects in the late-diagnosis group. T-tests were used to evaluate the differences between the groups in average measurements for height, weight, albumin, and hematocrit. Two sets of analyses were performed: one on the data from the time of diagnosis, and one on the data from the 2-year checkup.
To examine the effect of nutritional source (breastmilk vs. formula) of feeding at diagnosis on growth and nutritional parameters, the data were divided into breastfed and non-breastfed groups. There were 7 subjects that were breastfed prior to diagnosis, and 17 subjects that were not. Nutritional source of feeding at diagnosis was not noted for 7 subjects. Two sets of t-tests were also used to evaluate the differences between these groups.

Analyses of height and weight variables were performed using raw data transformed into standardized percentiles and z-scores. There is a great difference in "normal" height between a 2-week-old infant and a 52-week-old infant; therefore, the measurements had to be standardized to be useful. The checkups also did not occur for every patient exactly at the 2-year mark and consequently the only way to account for these variations was to use a standardized method of measurement. Both percentiles and z-scores are based on national average size-for-age data (13).

Regressions were run on the data to find the most predictive factors for height and weight at age 2 years. Each regression began with the same set of variables: gender, age at diagnosis, nutritional source of feeding at diagnosis, low albumin at diagnosis, low hematocrit at diagnosis, diagnosis suggested by malnutrition, diagnosis suggested by a family history of CF, and genotype. The irrelevant factors were then excluded until a working model revealed the most highly predictive factors.

Analyses of albumin and hematocrit were initially performed using raw data, but since normal raw albumin and hematocrit levels vary from age group to age group, these data were re-classified into binary variables: "normal/low". An albumin or hematocrit
value was classified as “normal” if it fell within the normal range for the patient’s age, as
defined by criteria established by Primary Children’s Medical Center (14). The value was
classified as “low” if it fell below the normal range.

Electrolyte and fat-soluble vitamin data were gathered as well. The data on
fat-soluble vitamins for the time of diagnosis were too sparse to use in an analysis, as
were electrolyte and fat-soluble vitamin data from the two-year checkup. Paired t-tests
were performed on the initial and final growth measurements within the early- and
late-diagnosis groups to determine if subjects had experienced a significant catch-up or
drop-off in growth before their 2-year checkups.

RESULTS

A total of 31 patients at the clinic met the inclusion criteria; 11 males and 20
females were included, and all but one (a Hispanic patient) were Caucasian. See Figures
1-3 for a summary of descriptive data for the entire group. As expected, most of the
subjects were Caucasian, with females making up the majority (N=20) of cases. The
diagnosis for more than a third of the cases was suggested either partially or completely
by the development of malnutrition and/or failure to thrive, and a diagnostic sweat
chloride test was available for 29 of 31 cases. The average age at diagnosis was 15.6
weeks (SD ± 13.8).

The analysis of the data when the cases were divided by nutritional source of
feeding revealed some unexpected results. There were no significant differences in any of
the nutritional or growth parameters between the breastfed children and the formula-fed
children, either at diagnosis or at the 2-year check-up. There was a near-significant result noted for the difference in weight percentile at diagnosis between the breastfed and formula-fed groups (p=0.081), but none of the analyses reached the 0.05 level of significance.

Using the early- and late-diagnosis groups for analysis, some interesting results were found. There were significant differences in the growth parameters between the groups at the time of diagnosis (see Tables 1 and 2). On average, the children diagnosed later were significantly smaller, both in weight (p=0.005) and height (p=0.000), at the time of their first checkup. At this checkup, there were also significantly more children in this late-diagnosis group who were at or below the 25th percentile for both height and weight (p=0.000).

There were also significant differences in nutritional parameters between the groups (see Tables 1 and 2). Significantly more children in the early-diagnosis group had low hematocrit (p=0.042), low albumin (p=0.005), and were low in both albumin and hematocrit (p=0.010). There were insufficient data to make an analysis for blood levels of fat-soluble vitamins.

At the final checkup, there were also significant differences between the early- and late-diagnosis groups. The early-diagnosis group was still significantly taller (p=0.017) than the late-diagnosis group, and still had significantly fewer subjects (p=0.014) who were at or below the 25th percentile for both height and weight. Nutritional data were very sparse; there were not enough data to make an analysis on any of the nutritional parameters at 2 years of age. The paired t-tests for initial and 2-year
growth measurements within the groups showed that the subjects had no significant
catch-up or drop-off in growth between diagnosis and age 2 years.

The regressions (N=24) found some predictive factors for growth at age 2 years
(Tables 3 and 4). Low albumin at diagnosis was a predictor for most of the growth
variables at 2 years of age. Low albumin at diagnosis was predictive of raw weight
(p=0.045), weight percentile (p=0.045), and height z-score (p=0.015), with low albumin
at diagnosis predicting increased weights and taller heights at the 2-year mark. Other
positive predictors of weight at 2 years of age included nutritional source of feeding (with
breastfeeding predicting a heavier weight) and a diagnosis suggested by a family history
of CF.

DISCUSSION

It was determined that the nutritional source (breastmilk vs. formula) had no
influence on nutritional or growth parameters. Human milk has a relatively low protein
content in comparison with formula, and it is logical that breastfed children with CF, who
may have problems with protein absorption, would have lower blood protein levels than
those who drink formula. This was not found to be the case. The literature suggests that
breastfed babies with undiagnosed CF have a greater tendency to develop
hypoalbuminemia, but the data in this study were too sparse to corroborate this finding.
The fact that there was no nutritional source noted for 7 of the 31 cases (22.6%) could
have had an effect on the outcome of the analyses, or it could be that there truly is no
difference between formula-fed and breastfed infants with undiagnosed cystic fibrosis.
As shown in this study, if undernutrition in children with CF is not caught and corrected early, serious consequences can result. Undernutrition is a serious issue which can result in a myriad of problems for young children. Growth failure, increased morbidity and mortality, and delayed development have been noted in malnourished children (4,15). Nutrient deficiencies are also associated with poor immune function and increased risk of respiratory infections in children with CF, and some connections to cognitive and intellectual impairment in undernourished children have been noted as well (16).

Malnutrition in infancy leads to measurable deficiencies in height and weight for height when examined years later (4). If intensive nutritional intervention is implemented, these parameters can be improved, but not completely corrected (15). Catch-up growth after severe malnutrition is difficult, if not impossible, but screening can prevent early stunting due to undiagnosed CF in many infants (17,18). In addition to stunting, a decreased weight for height is also associated with increased risk for mortality, especially in patients older than 18 years of age (19).

These results indicate that age at diagnosis has a large impact on growth, especially when comparisons are made at age 2 years. The children who were diagnosed after 9 weeks of age were comparatively shorter, and their height had not caught up with the heights of their early-diagnosis cohorts by 2 years of age. The weights of the children in the late-diagnosis group had caught up, but the majority remained below the 25th percentile in both height and weight. This agrees with the literature discussed earlier.
where early-diagnosed patients were larger and retained their growth advantage over their late-diagnosed cohorts (9).

Nutritional parameters had all equalized between the two groups by the final checkup as well. Since the early-diagnosis subjects were the ones with low albumin and hematocrit, those nutritional parameters do not seem to indicate a worse clinical course over time. Again, this concurs with the literature (6), but it may just indicate a more severe initial case of CF, which would trigger an earlier diagnosis due to development of malnutrition and other serious symptoms. This study supports the critical need for early diagnosis and treatment of CF.

In this study, malnutrition at diagnosis did not necessarily translate into growth deficiencies later in life. Early diagnosis identified those children who had low albumin, an indicator of CF. With this early diagnosis, nutritional intervention allowed these children to have more positive height/weight outcomes at 2 years of age than those children who were in the late diagnosis group.

Nutritional source of feeding at diagnosis had no long-term effect on growth accretion. Children with CF have some malabsorption of nutrients necessary for growth, especially before diagnosis, and human milk is naturally lower in protein than formula. It might be expected that the lower protein content of human milk, coupled with the increased protein needs for children with CF, would result in malnutrition being more prevalent in the breastfed group. However this study did not find this to be the case.
CONCLUSION

Nutritional source of feeding at diagnosis does not seem to impact growth or nutritional of children with cystic fibrosis, either at diagnosis or later in life. However, age at diagnosis of cystic fibrosis has significant influence on nutritional and growth parameters, both at time of diagnosis and at age 2 years. Children who were diagnosed later than 2 months of age remained shorter when evaluated at 2 years of age.

Low albumin at diagnosis was a positive predictor of growth at 2 years of age, due to early nutritional intervention, and highlights the critical need for early detection and treatment of malnutrition in CF to achieve optimal growth.

References


ABSTRACT

Purpose: A retrospective chart review was conducted to determine if age or nutritional source (breastmilk vs. formula) of feeding at diagnosis significantly affected growth accretion for children with cystic fibrosis at age 6 years. This study was also to determine if nutritional (or other) parameters measured at diagnosis were predictors of height and or weight at age 6 years.

Methods: Charts were reviewed for growth parameters for subjects with cystic fibrosis who were diagnosed between January 1, 1995, and December 31, 1997 and were 1 year of age or younger at time of diagnosis. Thirteen subjects met the inclusion criteria, but only 9 of those had both sufficient growth and nutritional data to be included in the analyses. Nutritional parameters included serum albumin, hematocrit, sodium, chloride, potassium, and fat-soluble vitamins A, D, and E. Growth parameters included height and weight (raw data, percentiles, and z-scores). ANOVA and regression were used to determine growth accretion and predictors.

Results: Children in the late-diagnosis group (N=6) had significantly lower growth accretion at age 6 years than their early-diagnosed (N=7) peers. Low albumin at diagnosis was predictive of better growth at age 6 years, because the children with low albumin
were also those who were diagnosed earlier. This could have led to more aggressive, earlier interventions and resulted in better growth in the early-diagnosis group.

INTRODUCTION

Cystic fibrosis (CF) is an inherited disorder that affects the exocrine glands of the lungs, gastrointestinal tract and sweat glands (1,2). The average age of diagnosis is 6 months, and milder forms of the disease are often diagnosed later in life (3,4). The majority of children are diagnosed before the age of 3 years due to the development of failure to thrive, severe respiratory or gastrointestinal complications (1,3-5). Early diagnosis and treatment may help alleviate or prevent these complications.

Cystic fibrosis patients with pancreatic insufficiency (PI) have an inadequate amount of digestive enzymes available in the gastrointestinal tract. The production of trypsin and lipases are the most severely affected, seriously hampering the digestion and absorption of protein and fat. This, in turn, can lead to malnutrition and poor growth in untreated children (6). Malnutrition and decreased body mass are markers of poor prognosis for patients, especially those with lung disease.

Malnutrition can develop in an infant with CF if the baby is fed human milk or formula. Human milk has a relatively low protein content that could contribute to malnutrition in children with CF, who have problems with nutrient absorption, especially in the absence of corrective enzyme therapy. Infants fed a soy-based formula can also develop malnutrition (7). While the soy formula has more protein, it is possible that the protein is less bioavailable (6). In spite of this, breast-fed and formula-fed infants with CF
can achieve similar growth rates and blood protein levels, apparently without the use of a protein supplement for the breastfed infants, when proper dosage of enzymes is achieved (8).

Patients with CF who are diagnosed early through screening tend to weigh more and be taller than their non-screened CF cohorts (9,10). This difference is especially evident in the group of CF patients with severe PI, because earlier replacement of pancreatic enzymes leads to improved nutrient utilization in the crucial early growth phases. These benefits continue into childhood, with early-diagnosed patients retaining their advantage in height and weight over their late-diagnosed cohorts (9). Infants who are diagnosed before symptoms develop and treated preventatively have the best prognosis (11), but some research has found no difference in height and/or weight between early- and late-diagnosis groups (12).

The purpose of this study was to determine growth accretion for children with cystic fibrosis at the age of 6 years, and to discover which (if any) nutritional or other parameters are predictors of growth at age 6 years in a Utah CF population that does not have newborn screening for CF. Effect of age at diagnosis and/or nutritional source (breastmilk vs. formula) of feeding at diagnosis was examined to uncover long-lasting effects on growth, especially to see if 6-year old children who were older than 2 months when diagnosed with CF remained shorter and/or lighter than those diagnosed earlier. A set of variables that can be measured at diagnosis that will predict growth at age 6 years was also sought.
MATERIALS AND METHODS

Subjects were chosen from patients at the Cystic Fibrosis Clinic at Primary Children’s Medical Center (PCMC). To be included in the study, a subject must have been born between January 1, 1995, and December 31, 1997, and must have been 52 weeks of age or younger at time of diagnosis. Date of diagnosis was determined to be either the date of the patient’s definitive positive sweat chloride test or (in the absence of a definitive sweat chloride test) the date of the child’s initial evaluation at the Cystic Fibrosis Clinic. The subject must have continued to come to the PCMC Clinic until the 6-year checkup, as evidenced by available growth measurements. See Table 6 for a summary of information for each subject.

No direct intervention was planned, and no person-to-person contact with the patients occurred. The information from the records was collected by clinic workers using a standardized form and completely blinded before being given to the researcher. All identifying information and markers were removed. There was no way to identify the patients from the information given to the researcher. Patient information was protected by keeping the data forms in a locked filing cabinet in the researcher’s office.

Data were collected for growth parameters at the appointment closest to the subject’s 6-year (312-week) birthday. Actual diagnosis frequently occurred 1 to 2 weeks before the initial evaluation, but the parameters of interest were not measured until the initial appointment. Therefore, the nutritional and growth measurements from the first appointment were used as the “diagnosis” measurements.
The data were divided into early- and late-diagnosis groups, with the cutoff point at 9 weeks. There were 7 subjects in the early-diagnosis group and 6 subjects in the late-diagnosis group. Repeated-measures ANOVAs were used to evaluate the differences between the two groups for height and weight accretion at 6 years of age. After analyzing these groups, the data were then re-divided into breastfed and formula-fed groups. There were 6 formula-fed infants and 3 breastfed infants at diagnosis, with nutritional source of feeding unknown for 4 infants. The repeated-measures ANOVAs were used to evaluate the differences in growth accretion at 6 years of age between these groups. The cases where nutritional source of feeding was unknown were excluded from this analysis.

Regression analysis was run on the data to find the most predictive factors for height and weight at age 6 years. Each regression began with the same set of variables: gender, age at diagnosis, nutritional source of feeding at diagnosis, low albumin at diagnosis, low hematocrit at diagnosis, diagnosis suggested by malnutrition, diagnosis suggested by a family history of CF, and genotype. The irrelevant factors were then excluded until a working model revealed the most highly predictive factors.

Analyses of height and weight variables were performed using raw data, standardized percentiles, and z-scores. There is a great difference in “normal” height and weight between a 2-week-old infant and a 52-week-old infant; therefore, the measurements had to be standardized to be useful. The checkups also did not occur for every patient exactly at the 2- and 6-year marks. The only way to account for these variations was to use a standardized method of measurement. Both percentiles and z-scores are based on national average size-for-age data (13).
Albumin and hematocrit data were classified into binary variables: “normal/low.” An albumin or hematocrit value was classified as “normal” if it fell within the normal range for the patient’s age, as defined by criteria established by Primary Children’s Medical Center (14). The value was classified as “low” if it fell below the normal range.

RESULTS

A total of 13 patients met the 6-year inclusion criteria. Of those 13 subjects, 7 were diagnosed before 9 weeks of age, and 6 were diagnosed after 9 weeks of age.

For the regression analyses, the number of participants for this study was 9, since not all the subjects who met the inclusion criteria had the necessary height and weight data available.

The analysis found some predictive factors for growth at age 6 years (Tables 3 and 4). Low albumin at diagnosis was a predictor for all of the weight variables, and was also predictive of raw height (p=0.000), height percentile (p=0.000), and height z-score (p=0.000). Weight at 6 years was predicted by gender, with males significantly heavier than females. A heavier weight at 6 years was also predicted by early diagnosis. Age at diagnosis, nutritional source of feeding, and a family history of CF were also predictors of height at 6 years of age.

In studying growth accretion, this study found that specificity was lost when standardized scores rather than raw data were used. Significant differences in growth were discovered when raw data was analyzed (Table 5), but these differences disappeared when the analysis was re-run with standardized measurements. Therefore, by using the
initial measurement as the starting point, the effect of varying ages at diagnosis was
eliminated.

As expected, there were significant differences in weight and height
measurements at each of the 3 different measurement times (diagnosis, age 2 years, and
age 6 years), since children naturally grow taller and put on weight as they age.
Examination of the ANOVA interaction factor of the model reveals if significant
differences in growth accretion exist between the early- and late-diagnosis groups, as well
as the breastfed and formula-fed groups.

Results indicated that an older age at diagnosis leads to lower growth accretion at
age 6 years. The interaction factor was significant for both weight (p=0.001) and height
(p=0.008) between the early- and late-diagnosis groups (see Table 5). This indicates that,
while both groups gained weight and height, the early-diagnosis group gained
significantly more weight and height than the late-diagnosis group. Nutritional source of
feeding at diagnosis did not appear to significantly impact growth accretion at age 6
years, since the interaction factors for weight (p=0.672) and height (p=0.440) were both
decidedly non-significant.

DISCUSSION

The final sample size for the 6-year-old age group was very small (N=9). This
makes it difficult to extrapolate results from this data to larger populations. The small
number of cases might have affected results, and the dearth of data at 6 years also made it
impossible to properly examine some variables, especially the biochemical data. This
study is valuable as a pilot study; the next phase would be to gather data from several centers (or to use children from a larger range of years) to get more cases, especially at the 6-year mark.

Malnutrition in infancy can lead to growth deficiencies when the children are examined years later (6). The literature indicates that if intensive nutritional intervention is implemented, these parameters can be improved, but not completely corrected (15). Catch-up growth after severe malnutrition is difficult, if not impossible (16,17). In addition to stunting, a decreased weight for height is also associated with increased risk for mortality, especially in patients with CF older than 18 years of age (18).

In this study, malnutrition at diagnosis did not necessarily translate into growth deficiencies later in life. Low albumin was predictive of higher weights and taller heights at 6 years of age, rather than lower weights and shorter heights. Early diagnosis identified those children who had low albumin, an indicator of CF. With this early diagnosis, nutritional intervention allowed these children to have more positive growth outcomes at 6 years of age than those children who were in the late diagnosis group. This implies that early screening for CF is helpful, if not critical, for proper growth and development in these children.

It was expected that children in the early diagnosis group would be taller and heavier than the late diagnosis group, and this was the case. Additionally, it was expected that the females would be lighter than the males, and again this was confirmed in this study.
Nutritional source of feeding at diagnosis had no long-term effect on growth accretion. Children with CF usually have some malabsorption of nutrients necessary for growth, especially before diagnosis, and human milk is naturally lower in protein than formula. It might be expected that the lower protein content of human milk, coupled with the increased protein needs for children with CF, would result in malnutrition being more prevalent in the breastfed group. However, this was not found to be the case in this study.

CONCLUSION

Accumulation of both height and weight was greater at age 6 years for those children who were diagnosed with CF before the age of 9 weeks. Low albumin at diagnosis was a predictor of growth at 6 years of age, but it predicted taller heights and greater weights rather than shorter heights and lighter weights due to the early nutritional treatments provided to this group. This indicates early diagnosis and correction of malnutrition is crucial and highlights the need for early detection and treatment of malnutrition in CF to achieve optimal growth.

References


Children who are diagnosed with CF after the age of 2 months appear to be at a disadvantage when compared with their peers who were diagnosed before 2 months of age. Not only do they begin on a smaller growth curve at time of diagnosis, they are still following that smaller curve when they reach 2 and 6 years of age. Late diagnosis means lower accretion of growth, both height and weight, and children who are diagnosed late do not catch up to their early-diagnosed peers. Biochemical parameters tend to normalize after diagnosis, but may be important in determining future growth.

An earlier study found that low albumin and hematocrit levels are common in CF patients at diagnosis, but the researchers concluded that those low levels did not appear to predict a worse clinical course over the long term (1). Results from this study indicate that, even though the patients may not have long-term nutritional deficiencies, albumin levels at diagnosis have an inverse relationship with growth at 2 and at 6 years of age. The lower albumin levels signaled early treatment, which resulted in better growth over the long term. This suggests that albumin levels at diagnosis may be a more important indicator of long-term growth prognosis than previously indicated.

Because the differences between the groups begin at such an early age, it would be advantageous to implement a neonatal screening program to catch CF cases very early in life, before deficiencies have time to develop. Newborn screening for CF was suggested about 30 years ago, and several methods have been employed over the years in an attempt
to determine the best screening method. Testing the meconium for albumin was done initially, but proved to be ineffective. In 1979, a method was developed that measured immunoreactive trypsinogen (IRT) levels in dried blood samples. A first sample is taken in the first few days of life, and if IRT levels in that sample are elevated, a second sample is taken at 6-8 weeks of life. If that sample is also elevated, a sweat chloride test is performed to determine if cystic fibrosis is present (2).

The IRT method is used alone or in combination with genetic screening for the \( \text{?F}508 \) mutation, and in spite of an observed decline in IRT levels as patients age, it is currently considered the “gold standard” for screening. Faster and more sensitive results can be achieved with combination testing, rather than waiting 6-8 weeks for a repeat IRT test (2).

Screening, especially utilizing this combination method, is extremely effective in identifying infants with CF. Since delayed diagnosis of cystic fibrosis appears to increase risk of poor growth, it would seem advantageous to adopt a neonatal screening program for CF in the state of Utah.

This work should be viewed as a pilot study of malnutrition in infants with undiagnosed cystic fibrosis. The small numbers in this study, especially at the 6-year mark, make it very difficult to extrapolate these findings to a larger population. In order to validate these findings and further elucidate the relationships between age at diagnosis, malnutrition, and growth in children with CF, further research (with larger population groups) should be conducted.

APPENDIX
Table 1. Differences in raw data growth and nutritional parameters between early and late diagnosis groups.

At time of diagnosis

<table>
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<th>Early</th>
<th>Late</th>
<th>Comparisons</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Weight %ile</td>
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<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Weight z-score</td>
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<td>0.63</td>
<td>-1.82</td>
</tr>
<tr>
<td>Height %ile</td>
<td>44</td>
<td>19</td>
<td>12</td>
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<tr>
<td>Height z-score</td>
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<td>0.68</td>
<td>-1.53</td>
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<td>Sodium mg/dL</td>
<td>137</td>
<td>2.1</td>
<td>138</td>
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<tr>
<td>Chloride mg/dL</td>
<td>105</td>
<td>3.4</td>
<td>103</td>
</tr>
<tr>
<td>Potassium mg/dL</td>
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<td>0.63</td>
<td>4.2</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>*</td>
<td>*</td>
<td>*</td>
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At age two years

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<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Weight %ile</td>
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<td>26</td>
<td>19</td>
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<tr>
<td>Weight z-score</td>
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<td>0.78</td>
<td>-1.29</td>
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<td>Height %ile</td>
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<td>17</td>
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<tr>
<td>Height z-score</td>
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<td>0.95</td>
<td>-1.24</td>
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<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Chloride mg/dL</td>
<td>*</td>
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<tr>
<td>Potassium mg/dL</td>
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<tr>
<td>Vitamin A</td>
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<tr>
<td>Vitamin D</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>*</td>
<td>*</td>
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* not enough data to make an analysis
Table 2. Differences in binary growth and nutritional parameters between early and late diagnosis groups.

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<tr>
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<th>Early #</th>
<th>Early %</th>
<th>Late #</th>
<th>Late %</th>
<th>t-value</th>
<th>p-value</th>
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<td>Ht &amp; wt &lt;25%ile</td>
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<td>13</td>
<td>14</td>
<td>82</td>
<td>-4.3</td>
<td>0.000</td>
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<tr>
<td>low hct</td>
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<td>100</td>
<td>14</td>
<td>78</td>
<td>2.2</td>
<td>0.042</td>
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<tr>
<td>low alb</td>
<td>7</td>
<td>88</td>
<td>5</td>
<td>29</td>
<td>3.4</td>
<td>0.003</td>
</tr>
<tr>
<td>both low</td>
<td>6</td>
<td>86</td>
<td>5</td>
<td>29</td>
<td>2.8</td>
<td>0.010</td>
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</table>

<table>
<thead>
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<th>Early %</th>
<th>Late #</th>
<th>Late %</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>25</td>
<td>12</td>
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<td>-2.6</td>
<td>0.014</td>
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<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
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<tr>
<td>both low</td>
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<td>*</td>
<td>*</td>
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</table>

* not enough data to make an analysis
### Table 3. Factors predictive of weight at 2 and 6 years of age.

<table>
<thead>
<tr>
<th>2 yr wt</th>
<th>R²</th>
<th>Factor</th>
<th>B</th>
<th>β</th>
<th>t</th>
<th>sig</th>
<th>N</th>
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<tbody>
<tr>
<td>adj 0.561</td>
<td>0.579</td>
<td>dxbrfed</td>
<td>0.016</td>
<td>0.424</td>
<td>2.732</td>
<td>0.013</td>
<td>24</td>
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<tr>
<td></td>
<td></td>
<td>dxfamx</td>
<td>1.145</td>
<td>0.372</td>
<td>2.531</td>
<td>0.020</td>
<td>24</td>
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<tr>
<td></td>
<td></td>
<td>lowalb</td>
<td>1.007</td>
<td>0.337</td>
<td>2.143</td>
<td>0.045</td>
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<tr>
<td>adj 0.422</td>
<td>0.472</td>
<td>dxbrfed</td>
<td>0.285</td>
<td>0.470</td>
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<td>0.011</td>
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<tr>
<td></td>
<td></td>
<td>dxagecat</td>
<td>6.711</td>
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<td>6.044</td>
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<td></td>
<td>lowalb</td>
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<td>1.690</td>
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<td>adj .934</td>
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<td>60</td>
<td>1.159</td>
<td>7.792</td>
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<td></td>
<td></td>
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<td>77.8</td>
<td>1.584</td>
<td>10.651</td>
<td>0.000</td>
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<tr>
<td>adj .848</td>
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<td>0.003</td>
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<td>lowalb</td>
<td>2.7</td>
<td>1.521</td>
<td>6.75</td>
<td>0.001</td>
<td>9</td>
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B values are unstandardized regression coefficients
β values are standardized regression coefficients

**Abbreviation Key**

| dxbrfed | Breastfed or formula-fed at diagnosis |
| dxfamx | Diagnosis suggested by a family history of CF |
| lowalb | Had low albumin value at diagnosis |
| gender | Male or female |
| dxagecat | Age at diagnosis (early or late) |
| 2 yr wt | Raw weight (in kilograms) at two years of age |
| 2 yr wtpct | Weight percentile at two years of age |
| 2 yr wt z | Z-score for weight at two years of age |
| 6 yr wt | Raw weight (in kilograms) at six years of age |
| 6 yr wtpct | Weight percentile at six years of age |
| 6 yr wt z | Z-score for weight at six years of age |
Table 4. Factors predictive of height at 2 and 6 years of age.

<table>
<thead>
<tr>
<th></th>
<th>$R^2$</th>
<th>Factor</th>
<th>$\beta$</th>
<th>t</th>
<th>sig</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr lg</td>
<td>0.344</td>
<td>dxbrfed</td>
<td>0.044</td>
<td>0.36</td>
<td>1.906</td>
<td>0.070</td>
</tr>
<tr>
<td></td>
<td>adj 0.282</td>
<td>lowalb</td>
<td>3.47</td>
<td>0.353</td>
<td>1.866</td>
<td>0.076</td>
</tr>
<tr>
<td>2 yr lgpct</td>
<td>0.346</td>
<td>dxbrfed</td>
<td>0.225</td>
<td>0.351</td>
<td>1.859</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>adj 0.284</td>
<td>lowalb</td>
<td>18.807</td>
<td>0.364</td>
<td>1.929</td>
<td>0.067</td>
</tr>
<tr>
<td>2 yr lg z</td>
<td>0.302</td>
<td>gender</td>
<td>0.719</td>
<td>0.384</td>
<td>2.046</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>adj 0.236</td>
<td>lowalb</td>
<td>0.878</td>
<td>0.495</td>
<td>2.639</td>
<td>0.015</td>
</tr>
<tr>
<td>6 yr lg</td>
<td>0.978</td>
<td>dxfamhx</td>
<td>3.746</td>
<td>0.352</td>
<td>4.822</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>adj 0.964</td>
<td>dxagecat</td>
<td>14.782</td>
<td>1.319</td>
<td>11.799</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lowalb</td>
<td>18.468</td>
<td>1.737</td>
<td>14.741</td>
<td>0.000</td>
</tr>
<tr>
<td>6 yr lgpct</td>
<td>0.928</td>
<td>dxbrfed</td>
<td>-0.71</td>
<td>-0.917</td>
<td>-6.711</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>adj 0.904</td>
<td>lowalb</td>
<td>75.058</td>
<td>1.175</td>
<td>8.595</td>
<td>0.000</td>
</tr>
<tr>
<td>6 yr lg z</td>
<td>0.898</td>
<td>dxbrfed</td>
<td>-0.025</td>
<td>-0.962</td>
<td>-5.899</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>adj 0.864</td>
<td>lowalb</td>
<td>2.455</td>
<td>1.129</td>
<td>6.922</td>
<td>0.000</td>
</tr>
</tbody>
</table>

B values are unstandardized regression coefficients
$\beta$ values are standardized regression coefficients

**Abbreviation Key**

- dxbrfed: Breastfed or formula-fed at diagnosis
- dxfamhx: Diagnosis suggested by a family history of CF
- lowalb: Had low albumin value at diagnosis
- gender: Male or female
- dxagecat: Age at diagnosis (early or late)
- 2 yr lg: Raw height (centimeters) at two years of age
- 2 yr lgpct: Height percentile at two years of age
- 2 yr lg z: Z-score for height at two years of age
- 6 yr lg: Raw height (centimeters) at six years of age
- 6 yr lgpct: Height percentile at six years of age
- 6 yr lg z: Z-score for height at six years of age
Table 5. Repeated measures ANOVAs for weight and height.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>F-value</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight accretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dxagecat</td>
<td>11.650</td>
<td>0.001</td>
</tr>
<tr>
<td>dxbrfed</td>
<td>0.410</td>
<td>0.672</td>
</tr>
<tr>
<td>height accretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dxagecat</td>
<td>7.048</td>
<td>0.008</td>
</tr>
<tr>
<td>dxbrfed</td>
<td>0.879</td>
<td>0.440</td>
</tr>
</tbody>
</table>

Significance values (p) are for the interaction factor of the model.
Table 6. Compendium of data for all subjects.

| Characteristic* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|----------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| low hematocrit at diagnosis | x | x | x | x | x | ? | x | x | x | ? | x | x | x | x | x | ? | x | x | x | x | ? | x | x | x | x | x | x | x |
| low albumin at diagnosis | x | x | ? | x | x | x | x | x | ? | x | x | ? | x | x | x | ? | x | x | x | x | ? | x | x | x | x | |
| malnourished at diagnosis** | x | x | ? | x | ? | x | ? | x | x | ? | x | x | ? | x | x | ? | x | x | x | x | ? | x | x | x | x | |
| early diagnosis (<9 weeks) | x | x | x | x | x | ? | x | x | x | ? | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| late diagnosis (>9 weeks) | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| breastfed at diagnosis | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| formula-fed at diagnosis | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| feeding unknown at diagnosis | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| included in 6-year data set | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| small for age at diagnosis*** | ? | x | x | x | x | x | x | x | x | ? | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| small for age at 2 years*** | x | x | x | ? | ? | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| small for age at 6 years*** | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| male | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| female | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

* an 'x' in the box indicates that this subject possessed this characteristic. A '?' indicates that the information was not available.
** malnourished at diagnosis = low in both hematocrit and albumin
*** the term 'small for age' means 'below the 25th percentile for both height and weight'
Figure 1. Factors suggesting diagnosis of cystic fibrosis (not mutually exclusive).
Figure 2. Genotype of participants.
Figure 3. Participants’ year of birth.