Pediatric Pulmonology 44:1223–1225 (2009)

Growth in Children With Cystic Fibrosis-Related Diabetes

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Summary. Cystic fibrosis-related diabetes (CFRD) is associated with a shortened life expectancy and greater deterioration in lung function than in CF patients with normal glucose metabolism. There are few published data on how CFRD affects growth in childhood. We carried out a retrospective case controlled study of growth and lung function in 34 children with CFRD attending three specialist centers in London. We found that for the 2 years leading to CFRD diagnosis (at a mean age of 13.1 years), the mean height velocity was significantly less compared to controls: 4.9 (standard deviation—SD 1.6) cm/year vs. 6.0 (SD 1.9) cm/year ($P = 0.005$). For the 2 years following diagnosis, height velocity remained significantly lower (3.4 (SD 2.2) cm/year vs. 4.4 (SD 2.2) cm/year, $P = 0.02$). Mean FEV_1 was reduced prior to diagnosis and at diagnosis, but was similar to controls 2 years after diagnosis. This study highlights the compromise in height velocity and lung function that occurs prior to diagnosis of CFRD in children with CF, and a reduction in height velocity should be considered an indicator of impaired glucose metabolism. It would be useful to know whether early treatment with insulin can help promote catch up growth. **Pediatr Pulmonol. 2009; 44:1223–1225.**

Key words: cystic fibrosis; diabetes; growth.

INTRODUCTION

Cystic fibrosis-related diabetes (CFRD) may be associated with a reduction in lung function and mean survival.[1] Early detection of CFRD is important as clinical status can deteriorate 2–4 years prior to its recognition and once treated with insulin, lung function may revert to the pre-diabetic state.[2] The current UK CF Trust recommendation is to screen children over 12 years annually with an oral glucose tolerance test,[3] but this is still controversial.[4]

Although CF is known to be associated with poor growth,[5,6] there are few data on the impact of CFRD on growth compared to CF children with normal glucose metabolism. It is also unknown whether treatment with insulin reverses any adverse effects on growth. The aim of this study was to assess growth velocity and lung function both prior to and following the diagnosis of CFRD in children and matched controls.

SUBJECTS AND METHODS

This was a retrospective study set in three specialist pediatric CF centers in London looking after a total of 600 children with CF. Diagnosis of CFRD was based on an abnormal oral glucose tolerance test (using standard World Health Organisation protocol of 2 hr plasma venous sample $\geq$7.8 to $<$11.1 mmol/L as impaired; with level $\geq$11.1 mmol/L diagnostic for diabetes),[3] followed by repeated elevated random blood glucoses $>$11 mmol/L ($>$198 mg/dl). All patients' diabetes was treated with subcutaneous insulin using varied regimens (dose and type) depending on the individual's glucose profile and response to treatment. Each patient with CFRD was matched for gender and age with another CF patient (without CFRD) from the same specialist center.

Patient data were collected from each center's computer database and patients' notes. Growth parameters, and lung function results (forced expiratory volume in 1 sec [FEV_1] and forced vital capacity [FVC]), for the 2 years preceding and 2 years following the diagnosis of CFRD were recorded. Similar data were recorded for the non-CFRD controls at a matched time. Height and weight measurements were converted to age- and gender-specific *Z*-scores on the basis of reference data published by the British standard reference ranges.[7] We did not attempt to gather data on adherence to insulin or pulmonary therapies.

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Received 8 May 2009; Revised 27 July 2009; Accepted 27 July 2009.

DOI 10.1002/ppul.21127
Published online 5 November 2009 in Wiley InterScience (www.interscience.wiley.com).

Differences between the CFRD and the control group were tested for significance using a paired *t*-test or a Wilcoxon test, as appropriate. Analysis of variance, paired *t*-tests or Wilcoxon tests were used to analyze changes before and after CRFD diagnosis. All tests were two-tailed, and a *P*-value <0.05 was considered significant. Ethical consent was obtained from the Thames Valley MREC (06/MRE 12/4).

RESULTS

There were 34 patients with CFRD (18 female) under 16 years old at the time of their CFRD diagnosis (mean age 13.1 years, range 7.5–15.9). This gives a point prevalence of 34/600, that is, approximately 6%. There were 34 controls (18 female) with mean age 13.1 years, range 8.1–16.0. Twenty-six (76%) were homozygous for $\triangle$F508 compared to 24 (71%) controls. All CFRD patients were pancreatic insufficient, compared to 33/34 controls. All patients but one (Asian) were Caucasian. Nine patients (26%) were diagnosed with CFRD under the age of 12 years, including four (12%) under 10 years. Of the patients who developed CFRD, 24 (71%) had failure to thrive as their initial presenting feature of CF, compared to 8 (24%) patients in the group who did not develop CFRD ($P < 0.0001$). Similarly, 22 (65%) of CFRD patients had respiratory symptoms (recurrent cough, wheeze and respiratory infections) at their initial diagnosis of CF compared to 11 (32%) of those who did not ($P < 0.0001$).

Height and weight *Z*-scores were not significantly different prior to, at diagnosis, or 2 years after diagnosis of CFRD, when compared to controls (Table 1). However height did tend to be lower in the CFRD patients 2 years post-diagnosis. For the 2 years leading to CFRD diagnosis, the mean height velocity was significantly less in those patients compared to controls (4.9 (SD 1.6) cm/year vs. 6.0 (SD 1.9) cm/year, $P = 0.005$). For the 2 years following diagnosis, height velocity remained significantly lower (3.4 (SD 2.2) cm/year vs. 4.4 (SD 2.2) cm/year, $P = 0.02$), see table. There is also a significant difference in height velocities comparing pre- and post-diagnosis (and matched times) $P < 0.005$ in both groups (Fig. 1).

FEV_1 was significantly reduced in patients with CFRD at 2 years prior to diagnosis and at diagnosis (Table 1). Two years after CFRD diagnosis, the FEV_1 was similar to controls. FVC was not different between the groups. The median annual fall in FEV_1 was 1.5% pre- and 1.4% post-CFRD diagnosis, matched to 2.3% versus 2.5% in the controls.

DISCUSSION

This retrospective case controlled study has shown that patients with CFRD had a significantly lower height

TABLE 1— Mean (SD) Growth and Lung Function Parameters for Patients With CFRD 2 Years Prior to, at the Time of, and 2 Years After the Time of CDRD Diagnosis, Compared With Matched CF Controls at Similar Times

		CFRD	Controls	*P*
Height (cm)	Pre-diagnosis	139.8 (14.4)	139.3 (12.1)	n.s.
	Diagnosis	149.8 (14.5)	150.9 (12.8)	n.s.
	Post-diagnosis	155.8 (13.1)	158.6 (12.2)	0.06
Height *Z*-score	Pre-diagnosis	−0.62 (1.1)	−0.74 (0.8)	n.s.
	Diagnosis	−0.80 (1.2)	−0.60 (0.8)	n.s.
	Post-diagnosis	−0.93 (1.1)	−0.51 (0.9)	0.05
Height velocity (cm/year)	At diagnosis	4.9 (1.6)	6.0 (1.9)	0.005
	Post-diagnosis	3.4 (2.2)	4.4 (2.2)	0.02
Weight (kg)	Pre-diagnosis	34.8 (11.3)	33.8 (8.4)	n.s.
	Diagnosis	42.1 (12.4)	43.4 (10.6)	n.s.
	Post-diagnosis	47.0 (12.2)	48.9 (14.1)	n.s.
Wt *Z*-score	Pre-diagnosis	−0.5 (1.1)	−0.5 (1.0)	n.s.
	Diagnosis	−0.6 (1.2)	−0.4 (1.1)	n.s.
	Post-diagnosis	−0.8 (1.2)	−0.6 (1.4)	n.s.
BMI (kg/m^2)	Pre-diagnosis	17.3 (2.7)	17.1 (2.0)	n.s.
	Diagnosis	18.4 (2.1)	18.7 (2.5)	n.s.
	Post-diagnosis	19.0 (2.8)	19.0 (3.1)	n.s.
BMI *Z*-score	Pre-diagnosis	−0.2 (1.1)	−0.03 (1.0)	n.s.
	Diagnosis	−0.2 (1.1)	−0.02 (1.1)	n.s.
	Post-diagnosis	−0.4 (1.1)	−0.40 (1.3)	n.s.
Mean FEV_1 (% predicted)	Pre-diagnosis	77 (21)	87 (21)	0.05
	Diagnosis	72 (21)	81 (18)	0.04
	Post-diagnosis	70 (22)	77 (22)	n.s.
Mean FVC (% predicted)	Pre-diagnosis	84 (19)	92 (17)	n.s.
	Diagnosis	84 (18)	91 (13)	0.07
	Post-diagnosis	83 (21)	89 (19)	n.s.

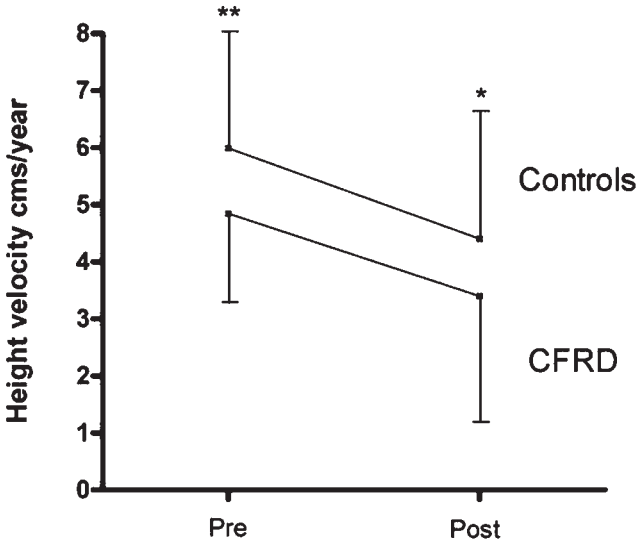

Fig. 1. Mean height velocity in cm/year in patients for CFRD and matched controls (bars indicate SD) for the 2 years prior to and 2 years following CFRD diagnosis. Patients with CFRD have a lower height velocity both pre ($P < 0.005$) and post- (*$P < 0.05$) diagnosis. There is also a significant difference in height velocities pre- versus post-diagnosis ($P < 0.005$) in both groups.**

velocity than non-diabetic controls for the 2 years prior to diagnosis of their diabetes, and this was still the case 2 years after insulin therapy was initiated. This suggests that current insulin regimens are not adequate to allow catch up in height, or perhaps that insulin treatment should be considered earlier. There was no statistical difference in height, weight, or BMI between the two groups, although these values tended to be lower both at the time of diagnosis and 2 years later in the CFRD patients. It is possible these differences did not reach significance due to the relatively small numbers (type II error) combined with the wide age variation and SD of the measurements.

One problem with our study is that height velocity may be difficult to interpret as children enter their pubertal growth spurts at different times,[8,9] and we do not have valid data on pubertal staging for our study. Unfortunately formal assessment of puberty is done poorly if at all in most CF centers. Children with CF have delayed puberty,[10] and although this may be more pronounced in patients with CFRD, which would then account for some of the differences in height velocity, there are no data to support this, nor is this our clinical experience. Nevertheless the difference in height velocity noted may be due to impaired glucose metabolism effecting pubertal onset, and/or height velocity directly (irrespective of puberty). This study cannot answer which it is but we have at least demonstrated there is an effect. On balance though we believe that the differences in height velocity may be due to the metabolic effects of low insulin levels in the pre-diagnostic stage. It would be important to follow these children to final height to establish if residual height differences have occurred as a consequence of CFRD, or if after a delayed pubertal growth spurt any differences were eradicated.

The lung function (FEV_1) of the CFRD patients was also significantly lower both 2 years before and at the time of CFRD diagnosis, but this improved so that 2 years after treatment was started; it was no longer different from the matched controls. This is in line with other studies in adults showing deterioration of lung function prior to and in association with CFRD with some improvement after therapy.[2,11]

This study demonstrates the impact of CFRD on growth during childhood and adolescence, with deterioration in height velocity for the 2 years before a diagnosis of CFRD. A significant number of children developed CFRD before the current recommended screening age of 12 years. Insulin treatment for 2 years had a positive effect on lung function but did not restore height to that of controls without CFRD. In children with CF, unexplained weight loss and reduced lung function, are often taken as warning signs of impaired glucose metabolism, we suggest that a reduction in height velocity should also be an indicator.

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