Abstract

Objective: Growth delay in cystic fibrosis is frequent and is usually the result of several interacting causes. It most often derives from severe respiratory impairment and severe malabsorption. There are however patients whose clinical condition is not severe enough to be held accountable for this phenomenon. We aimed at describing patients who showed growth delay, who were not affected by severe pulmonary disease or malabsorption and who, when tested, showed a reduced GH secretion after stimulation with conventional agents. We noticed a disproportionately large prevalence of growth hormone (GH) release deficit (GHRD) in pediatric cystic fibrosis (CF) patients.

Patients and methods: We examined all patients under our care in the period 2006–11, who were older than 5 and younger than 16 years old. We focussed on those who fell below the 3rd height percentile, or whose growth during the previous 18 months faltered by $N2 SD$, and who did not present clinical conditions that could reasonably explain their failure to thrive. These patients were subjected to standard GH provocative tests.

Results: Out of 285 who matched the age criterion, 33 patients also matched the height percentile criterion. While 15/33 suffered clinical conditions that could reasonably explain their failure to thrive, 18/33 underwent GH release provocative tests and 12/18 showed a release deficit.

Conclusions: We conclude that impaired GH secretion is more frequent among CF patients compared to the prevalence of GH deficiency in the general population and that GH release impairment may be an independent cause of growth delay in CF. Our findings are in agreement with recent studies that have described low GH levels in CF piglets and in neonates with CF [1].

Keywords: Cystic fibrosis; Growth hormone; Growth retardation; Growth hormone deficiency

1. Introduction

Monitoring growth is a priority in the clinical management of cystic fibrosis (CF) patients.

Poor linear growth in patients affected by CF is generally thought to be caused by concomitant severe complications (pulmonary disease, malabsorption, diabetes, etc.). Although it is certainly true that these clinical conditions affect growth (and we have recently documented the correlation between low growth and reduced long-term lung function in CF), it is also true that reduced growth may be present in patients whose clinical condition is not severe enough to be held accountable for this phenomenon [2,3].
In the follow-up of CF patients failing to thrive, we were struck – at two centers in Italy and one center in Israel – by what appears to be a relatively high prevalence of growth hormone (GH) release deficiency. We wish to describe the GH deficient patients under our care and to discuss the potential mechanisms involved.

Though there have been several trials investigating the effects of growth hormone therapy in CF patients (see Hardin [4] for an exhaustive review) showing that it may be beneficial in CF patients without a demonstrable GH deficit, this is the first study to assess the CF population for the presence and prevalence of true GH release deficiency.

2. Patients and methods

The cystic fibrosis centers of Verona (Italy), Brescia (Italy) and Petah Tikva (Israel) participated in this study. Each center director reviewed patients’ records to ascertain the prevalence of growth retardation. All patients attending the centers in the period 2006–2011, who were older than 5 and younger than 16 years old, were included.

CF was diagnosed based on commonly accepted criteria, i.e. abnormal chloride sweat test (>60 mEq/l), and the presence of disease-causing mutations as well as typical clinical manifestations [5].

We only included patients [1] whose nutrition level was considered adequate, with normal caloric intake [2], whose pancreatic insufficiency was adequately corrected by pancreatic enzymes supplementation to reach no steatorrhea, even in the presence of a low body mass index (BMI) [3], without severe liver abnormalities [4], whose pulmonary disease was not severe, defined as Forced expiratory volume in one second (FEV1) <60% of predicted [5], who were not on high dose steroids (defined as prednisone >1 mg/kg daily) for longer than 1 month during the previous 6 months. We also excluded patients with [1] celiac disease [2], CF related diabetes [3], reflux gastroesophageal disease [4], milk protein intolerance or [5] other conditions associated with growth retardation.

Relevant tests and measurements were height, height percentile based on the Center for Disease Control and Prevention (CDC) charts [6] height velocity, body mass index, and body weight. Neonatal length and body weight and gestational age at birth were recorded where available. Growth deficit was defined as height below the 3rd percentile. Bone age was assessed based on the Tanner–Whitehouse 3 (TW3) method [7]. IGF-1 SD-scores were calculated based on Clayton PE [8]. Brain MRI was performed to ascertain pituitary abnormalities.

GH release stimulation tests were done per standard clinical care at each of the centers with two commonly accepted agents. Each child was tested twice (with arginine and insulin at Verona, with arginine and clonidine at Brescia, with clonidine and glucagon at Petah Tikva). Arginine was administered to fasting patients at 0.5 g/kg (max 30 g) intravenously over 30 min. Sampling was done at −30, 0, 30, 60, 90 and 120 min. Clonidine was administered to fasting patients at 0.15 mg/m² orally with blood drawn at 0, 30, 60, 90, 120 and 150 min. Insulin was administered at 0.08 IU/kg (max 2 IU) i.v. to fasting patients with blood drawn at −15, 0, 10, 15, 20, 30, 60 min [9–11].

Patients were considered to be GHRD if both tests gave peak GH values below 10 ng/ml, according to the most recent published guidelines, i.e. the GH Research Society guidelines for the diagnosis and treatment of GH deficiency in childhood and adolescence [12].

All patients gave their informed consent to their data being treated anonymously for the purpose of the present report. The study protocol was approved by the Institutional Review Board of the hospital of Verona as this was the institution of the principal investigator.

3. Results

In total, 285 patients between 5 and 16 years of age were followed at our three centers during the period 2006–11. Of these patients, 33 showed a growth deficit as defined above. All patients were prepubertal.

Of these 33 patients, 15 suffered clinical conditions that could reasonably explain their failure to thrive (see above for exclusion criteria). GH release was tested only in the remaining 18 patients and found to be abnormally low in 12. Table 1 shows that patients had normal weight and length for gestational age at birth. Table 2 shows that all patients exhibited severe growth retardation as

<table>
<thead>
<tr>
<th>Gender</th>
<th>Gestational age (wk)</th>
<th>Weight (g and percentile)</th>
<th>Length (cm and percentile)</th>
<th>Sweat chloride (mEq/l)</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>39</td>
<td>3310 45</td>
<td>52.0 87</td>
<td>91</td>
<td>1717-1 G/A/F508del</td>
</tr>
<tr>
<td>2 F</td>
<td>38</td>
<td>3225 66</td>
<td>49.5 66</td>
<td>106</td>
<td>F508del/G85E</td>
</tr>
<tr>
<td>3 M</td>
<td>39</td>
<td>3870 92</td>
<td>50.0 46</td>
<td>120</td>
<td>F508del/N1303K</td>
</tr>
<tr>
<td>4 F</td>
<td>40</td>
<td>2740 7</td>
<td>46.0 2</td>
<td>95</td>
<td>F508del/F508del</td>
</tr>
<tr>
<td>5 F</td>
<td>38</td>
<td>2990 43</td>
<td>49.0 56</td>
<td>97</td>
<td>F508del/991delI5</td>
</tr>
<tr>
<td>6 F</td>
<td>38</td>
<td>2550 10</td>
<td>47.0 19</td>
<td>113</td>
<td>2183AA G/N1303K</td>
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<td>7 F</td>
<td>36</td>
<td>3010 83</td>
<td>49.0 85</td>
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<td>I507del/711+5 G A</td>
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<td>8 F</td>
<td>41</td>
<td>4100 97</td>
<td>52.0 50</td>
<td>113</td>
<td>F508del/W1282X</td>
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<tr>
<td>9 M</td>
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<td>2720 3</td>
<td>47.0 2</td>
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<td>F508del / F508del</td>
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<tr>
<td>10 F</td>
<td>40</td>
<td>3700 84</td>
<td>46.0 3</td>
<td>120</td>
<td>F508del/W1282X</td>
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<tr>
<td>11 M</td>
<td>38</td>
<td>2800 15</td>
<td>Not available</td>
<td>103</td>
<td>S549N/W1282X</td>
</tr>
<tr>
<td>12 M</td>
<td>42</td>
<td>3500 52</td>
<td>Not available</td>
<td>95</td>
<td>5 T/unknown</td>
</tr>
</tbody>
</table>
reflected by low weight and height values. Table 3 shows the peak GH values after stimulation, which was very low in some patients and lower than 10 mg/l in all of them. IGF1 was available in 10/12 patients. Six values were below the median value for age. Pituitary MRI was normal in all patients for site, volume and parenchyma.

All 12 patients with an abnormal GH response were started on commercially available rhGH as per standard prescribing information, i.e. 0.033 mg/kg/day subcutaneously for 6 days/week. In those patients who completed 1 year of treatment with rhGH height velocity showed a marked improvement. FEV1 improved in 3/6 and remained stable in the others.

Since five of the 12 patients started less than 1 year ago, follow-up data are only available for 7 patients. They are summarized in Table 2. None of these patients experienced pubertal growth spurt.

All patients followed at our centers undergo routine glucose tolerance tests yearly and blood glucose levels were monitored as per hrGH standard prescribing information. We used test strips at home and glycated hemoglobin measurements at our centers without detecting any significant adverse reactions to rhGH.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics at the time of testing.</th>
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<tbody>
<tr>
<td>Age at testing (year/month)</td>
<td>Height (cm and percentile)</td>
</tr>
<tr>
<td>1 11 y 0 m</td>
<td>130.0 1</td>
</tr>
<tr>
<td>2 6 y 7 m</td>
<td>108.0 2</td>
</tr>
<tr>
<td>3 7 y 3 m</td>
<td>108.5 0</td>
</tr>
<tr>
<td>4 11 y 8 m</td>
<td>135.5 3</td>
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<tr>
<td>5 11 y 11 m</td>
<td>135.5 2</td>
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<tr>
<td>6 10 y 11 m</td>
<td>130.0 2</td>
</tr>
<tr>
<td>7 12 y 0 m</td>
<td>136.0 1</td>
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<tr>
<td>8 10 y 10 m</td>
<td>126.7 1</td>
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<tr>
<td>9 8 y 7 m</td>
<td>115.0 0</td>
</tr>
<tr>
<td>10 9 y 3 m</td>
<td>121.6 2</td>
</tr>
<tr>
<td>11 4 y 6 m</td>
<td>92.0 0</td>
</tr>
<tr>
<td>12 7 y 11 m</td>
<td>110.4 0</td>
</tr>
</tbody>
</table>

n.a. = not available because patients have not yet reached 1 year of treatment.

4. Discussion

Three large CF centers independently noted among their patients a surprisingly high prevalence of patients with GHRD. Each center followed internationally accepted guidelines and tested GH release using two commonly accepted agents, differing only in the ones they chose. In our cohort of 285 CF patients, we tested 18 and found 12 with GH release deficit. Prevalence of patients with GHRD in the general population is consistently reported to be in the 0.02–0.03% range [13,14]. Prevalence in our CF patient population was at least 12/285 or 4.21%, i.e. 200 times as high. Since we tested only the 18 patients for whom the test appeared to be indicated and did not screen all patients in our cohort of 285 CF patients, it is still possible that we missed a few GHRD cases, making true prevalence even higher.

Poor linear growth in patients affected by CF is generally thought to be caused by concomitant severe complications (pulmonary disease, malabsorption, etc.). However, evidence suggests that even individuals with good clinical status do not reach their full growth potential [2,15] and infants with CF have been reported to be smaller than unaffected infants already at birth [16–18]. In a study on 89 CF patients detected by neonatal screening one third was found to be below the 3rd height percentile and one half were found to be below the 10th percentile [19]. Since the majority of infants with CF (except those with meconium ileus) are asymptomatic at birth, it is likely that prenatal and genetic factors directly influence growth.

CF patients show reduced growth even after appropriate treatment is started. Lai et al. [20] found that approximately 40% of infants were below the 5th percentile for weight and length at the time of diagnosis, but deficits in length/height and weight continued to be seen until adulthood, even after catch-up growth had been induced by aggressive management. This was confirmed in other studies [21–24].

Mice with a null mutation in CFTR were found to be severely growth retarded in weight and length compared with wild-type controls [25]. Rogan et al. [1] reported that, like humans, CF pigs were smaller than non-CF littermates.
Showing that GH release is reduced, at least in a small proportion of CF children, our data are in agreement with the hypothesis that the somatotropic axis is affected by CFTR malfunctioning. Previous studies have shown inconsistent data on GH levels, basal and after stimulation, in CF patients: for a review see Laursen et al. [26]. It should be noted that in those earlier studies patients had widely variable conditions and included patients with or without growth delays. Methods applied were also very different. Since GH effects on growth are prevalently mediated by IGF1, and circulating IGF1 levels are more stable, most of the attention has been focused on this hormone, which has been consistently found to be lower in CF (in human and in animal models) [1,25,27,28]. However, IGF1 levels vary greatly according to gender and age [8,29] and although several of our patients had IGF1 levels in the lower normal range, their number was too small to shed more light on the role of IGF1 in CF.

We speculate that GH deficiency might be directly related to the basic defect in CF. As recently shown by Hodges et al. [30] in an animal model, loss of CFTR function in neurons may result in poor growth and endocrine dysfunction. Rogan et al. [1] also found that forskolin induced GH release from cultured pituitary slices from CF pigs to a larger extent than from non-CF pigs, suggesting that lack of CFTR impairs release of GH. Based on their findings, they speculated that alterations in the somatotropic axis in CF may explain why individuals with good clinical status do not reach their full growth potential.

It is still under discussion whether CF patients may benefit from treatment with rhGH as a non specific anabolic agent. Published studies of GH use in children with CF have demonstrated significant improvement in height velocity and height Z score. Several reports suggest that GH treatment also results in improved forced vital capacity, and multiple studies have found improved clinical status as measured by decreased hospitalizations and courses of intravenous antibiotics. In general recombinant human GH improved almost all intermediate measures of pulmonary function, height, and weight in patients with CF. These studies have been reviewed by Hardin et al. [4] and more recently by Phung et al. [31]. The results of another trial were published more recently [32] showing that treatment with rhGH in prepubertal children with CF was effective in promoting growth, weight, lean body mass, lung volume, and lung flow rates, and concluding that in CF its anabolic actions might be beneficial. Respiratory function generally improved after 1-year rhGH in our patients, but this was not the main aim of the treatment.

We believe that intensive screening of CF patients to identify those with GH activity impairment is warranted in order to provide replacement treatment promptly for those who are more likely to benefit from GH supplementation.

5. Conclusions

We found an increased prevalence of GH deficiency in CF patients. Future studies are now needed to evaluate whether this GH deficiency in CF is directly related to defective CFTR or secondary.

In the mean time, we recommend to test all CF patients under the 3rd percentile for GH deficiency.

Acknowledgments

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References