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Original Article

Growth retardation and reduced growth hormone secretion in cystic fibrosis. Clinical observations from three CF centers

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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 >2 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].

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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 (FEV_1)<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/m^2 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 1
Characteristics at birth and at CF diagnosis (M = male, F = female).

	Gender	Gestational age (wk)	Weight (g and percentile)		Length (cm and percentile)		Sweat chloride (mEq/l)	Mutations
1	M	39	3310	45	52.0	87	91	1717-1 G A/F508del
2	F	38	3225	66	49.5	66	106	F508del/G85E
3	M	39	3870	92	50.0	46	120	F508del/N1303K
4	F	40	2740	7	46.0	2	95	F508del/F508del
5	F	38	2990	43	49.0	56	97	F508del/991del5
6	F	38	2550	10	47.0	19	113	2183AA G/N1303K
7	F	36	3010	83	49.0	85	99	I507del/711+5 G A
8	F	41	4100	97	52.0	50	113	F508del/W1282X
9	M	40	2720	3	47.0	2	141	F508del / F508del
10	F	40	3700	84	46.0	3	120	F508del/W1282X
11	M	38	2800	15	Not available	–	103	S549N/W1282X
12	M	42	3500	52	Not available	–	95	5 T/unknown