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Growth Failure in Focal Dermal Hypoplasia

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Abstract

Focal Dermal Hypoplasia (FDH) is a rare genetic disorder caused by mutations in the *PORCN* gene located on the X chromosome. Short stature was previously noted to be a common finding in FDH, however the etiology of this is unclear. The present study sought to elucidate specific causes for short stature by assessing growth charts, determining bone ages and auxologic measurements, examining laboratory data for the common causes of growth failure, assessing dietary intake, and performing a growth hormone stimulation test. Sixteen patients with FDH between the ages of 3 and 18 years of age consented to the study. While 11 out of 16 patients had short stature based on height less than 2 standard deviations below mid-parental target height percentile and bone age not suggestive of likely catch up growth, only 4 had a BMI less than the 5th percentile for age. Laboratory studies did not support a gastrointestinal, allergy or autoimmune cause of growth failure. Three patients had results suggestive of possible growth hormone deficiency. Although short stature is a common feature in FDH, our data suggests that severe undernutrition is not common in this group and that there may be underlying treatable causes for this short stature in some patients.

Keywords

Focal dermal hypoplasia; Goltz-Gorlin syndrome; growth hormone deficiency; pituitary deficiency; short stature

INTRODUCTION

Focal dermal hypoplasia (FDH), also known as Goltz-Gorlin Syndrome, is a rare genetic disorder that is a subset of the ectodermal dysplasias. It is caused by pathologic mutation or, less commonly, deletions of the *PORCN* gene on Xp11.23 and is transmitted as an X-linked dominant trait (Grzeschik et al., 2007). While the exact function of *PORCN* is not known, it is believed to be involved in the processing and release of Wnt proteins. There is significant phenotypic variation in patients with FDH, which may be attributable to variance in X-inactivation and somatic mosaicism. Genotype-phenotype correlation has not been seen (Maas et al., 2009). Clinical manifestations include skin and nail changes, eye anomalies, facial dysmorphism, abdominal wall defects and limb anomalies (Goltz, 1992; Goltz, Peterson, Gorlin, & Ravits, 1962). In a preliminary study conducted in March 2013, we noted height and weight deficits in our group of 19 individuals with FDH and found that this was a major concern for parents (Motil, Fete, & Fete, 2016). Since there are many factors that impact growth in children, including nutritional, hormonal and concurrent disease states, we sought to delineate specific causes for the short stature seen in children with FDH. In particular, we evaluated two pituitary functions (growth hormone and cortisol regulation) given that the pituitary gland develops from embryonic ectoderm and that Wnt signaling is important for pituitary growth and development and therefore may be impacted by *PORCN* mutations. Growth hormone deficiency has been reported in another ectodermal dysplasia syndrome, ectrodactyly-ectodermal defects and cleft lip/palate syndrome 1 (Knudtson & Aarskog, 1987).

MATERIALS AND METHODS

The National Foundation for Ectodermal Dysplasias (NFED) maintains a registry for Ectodermal Dysplasias which included 66 patients with FDH, 37 of whom were 3–18 years old in 2015. All children age 3–18 years in attendance at the NFED Annual Family Conference in 2015 who had the clinical diagnosis of FDH were eligible to participate. The diagnosis of FDH was based on review of medical records and clinical evaluation by physician members of the NFED Scientific Advisory Committee. The physicians who confirmed the diagnosis of FDH knew each patient. In total, 16 individuals, 14 females and 2 males participated in this study. The Colorado Multiple Institutional Review Board approved the research study. Informed consent was obtained for all participants. Families were requested to provide growth charts from their primary care provider as well as a 3-day food diary upon enrollment in the study. Daily dietary nutrient intakes were estimated using a nutrient database (The Minnesota Nutrition Data System, Version 4.02, Minneapolis, MN) and expressed as percentage of total energy intake or as percentages of the Dietary Reference Intake (DRI) for age and gender as published by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences. All subjects were admitted to the Children's Hospital Colorado Clinical Translational Research Center (CTRC) on July 22, 2015, for baseline laboratory screening for occult causes of growth failure, a bone age radiograph and a glucagon stimulation test to evaluate cortisol and growth hormone secretion. In the patients who consented to the phlebotomy portion of the study, baseline fasting venous samples were obtained for CBC, C-reactive protein, erythrocyte sedimentation rate (ESR), 25-hydroxy vitamin D, complete metabolic panel, pre-albumin,

vitamin E, Tissue Transglutaminase (TTG) IgA and total IgA, IgE, RAST panel for common food allergens, free thyroxine (free T4) and thyroid stimulating hormone (TSH), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGF-BP3), growth hormone and cortisol levels. Vitamin E level was checked as a surrogate for fat malabsorption. In patients who consented and had an IV placed, Glucagon (0.05 mg/kg up to 1 mg max) was administered subcutaneously and blood samples were drawn at 120 and 150 minutes for growth hormone and cortisol levels (Carillo & Bao, 2007). Blood samples were analyzed by standard clinical methods in the CTRC Core Lab and University of Colorado laboratories.

Height to the nearest tenth of a centimeter and weight to the nearest tenth of a kilogram were obtained by direct measurement using a calibrated Harpenden stadiometer and electronic scale. Heights and weights are reported as percentile for age based on the CDC 2000 growth curves. Birth length and weight, as well as previous growth measurements were ascertained from parent recall or available medical records. Physical exams were performed by physicians on the study team. Mid-upper arm circumference (MUAC) and skinfold thickness at the triceps, biceps, subscapular and suprailiac regions were measured by trained personnel (KM, TF). MUAC and triceps skinfold thickness percentiles or z-scores were calculated based on age and gender-appropriate reference data (Abdel-Rahman, Bi, & Thaete, 2017; Frisanco, 1981). Body fat, expressed as a proportion of body weight, was calculated from the triceps, biceps, subscapular and suprailiac skinfold thickness measurements (Durnin & Rahaman, 1967).

Bone age radiographs of the left hand were obtained for each participant and were read independently by 2 pediatric endocrinologists (SB and SH) according to the standards of Greulich and Pyle (Greulich, 1950). Short stature was defined as current height more than 2 standard deviations below mid-parental height percentile or final height prediction that was more than 2 standard deviations below mid-parental height based on bone age. The number of patients able to be classified into a group per parameter differed depending on whether there were data for the specific parameter for each patient. Mid parental height was calculated from reported parental heights using the following formula: (Maternal height (+13 cm if patient was male) + Paternal height (-13 cm if patient was female))/2.

A survey questionnaire was given to each family to query clinical symptoms and diagnoses associated with common growth, nutritional and GI complaints as well as any nutritional interventions.

Statistics: Data were recorded in a REDCAP (Harris et al., 2009) data base. As IGF1 and IGFBP3 vary by age, z-scores for both variables were calculated from assay data and used for further inferences. Wilcoxon tests were used to compare variables in participants with growth failure to those without. Logistic regression was used to test whether the IGF-1 and IGF-BP3 z-scores were significantly associated with short stature. However, as the sample size was small, the models did not converge and results could not be reported.

RESULTS

Sixteen patients with FDH (14 female, 2 male) with a mean age of 9.7 years $\pm$ 4.3 years (median 9.3 years, range 3–17.5 years), enrolled in the study. Median height percentile for age was 2.2% (25th percentile=0.8%, 75th percentile=6.2%) with 3 patients over the 50th percentile and 11 patients under the 3rd percentile for age (Table 1). Median weight percentile for age was 2.3% (25th percentile = <0.01%, 75th percentile=13.9%) resulting in a median BMI percentile for age of 26.3% (25th percentile = 3.8%, 75th percentile=37%). Only four of the patients had a BMI percentile that was less than the 5th percentile for age. Bone ages were not significantly delayed (>2 s.d.) compared to chronological age and 3 patients had advanced bone ages. Eleven out of 16 patients had short stature based on height more than 2 standard deviations below mid-parental target height percentile and bone age not suggestive of likely catch-up growth (Figure 1). Of the patients with short stature, 8/11 had a BMI $\geq$ 5th percentile for age. No reasons for short stature were identified on physical exam.

Based on parental responses to the questionnaire, 75% of parents perceived their child as underweight and 81% felt that their child was short. None of the patients reported celiac disease, which was confirmed by lack of Tissue Transglutaminase IgA antibodies in the 11 patients who had blood drawn (data not shown). Three patients reported food allergies, though only one of these patients consented to the blood draw. That patient had mildly elevated RAST to egg white and cow's milk, of which the family was already aware. Five patients reported use of supplemental formulas as noted in Table 2. Two patients had used a gastrostomy tube for feedings in the past. Seven out of 16 patients reported constipation.

Twelve participants completed 3-day food records. On average, dietary energy intakes were approximately 16% less than the amount expected to meet total daily energy expenditure for age; 37% of total daily energy intake was from fat and 50% of total daily energy intake was from carbohydrates (data not shown), which is in line with recommendations from the American Heart Association. Average dietary calcium intakes were about 35% less than the recommended dietary allowance for age (data not shown) and dietary intakes of vitamin D were 28% of the recommended amount for age (Table 2). Dietary protein (178% of recommended dietary intake) and micronutrient [iron (100% of recommended amount) and zinc (101% of recommended amount)] intakes met or exceeded the recommended dietary allowances for age in our study group.

Eleven of the 16 patients consented to blood draws. From the baseline blood chemistries, no patients had abnormalities in their electrolytes, liver transaminases or blood counts that would account for short stature or growth failure (data not shown). Vitamin D stores as measured by a 25-hydroxy Vitamin D level were low (defined as <30 ng/ml) in 5/11 patients, with 2 patients <20 ng/ml and 3 patients 20–30 ng/ml (Table 2). This did not correlate with vitamin D intake, suggesting that endogenous vitamin D production and/or unreported sources of vitamin D are significant in a number of the patients (Table 2). None of the 11 patients had low Vitamin E levels (data not shown).

For the entire study group, the mean percent body fat was 22 $\pm$ 7% based on skinfold thickness measurements. Comparing our 14 females with FDH to the average body fat for age values for healthy girls (Deurenberg, Pieters, & Hautvast, 1990; Slaughter et al., 1988), FDH girls had 4 $\pm$ 3% lower body fat, $p < 0.001$. Mid upper arm circumference (MUAC) values are noted in Table 2 as z-scores to provide additional information on nutritional state, with z-scores -1 to $+1$ indicative of average nutritional status.

Insulin-like growth factor 1 (IGF-1) and its associated carrier Insulin-like growth factor binding protein 3 (IGF-BP3) are commonly used surrogates for growth hormone status since their production is stimulated by growth hormone and they are relatively stable in the serum. Ten out of 11 patients had IGF-1 levels within the normal range for age and all 11 patients had IGF-BP3 levels within the normal range for age (data not shown).

IGF-1 and IGF-BP3 z-scores did not differ between the short stature and normal stature groups (Table 3). BMI percentile, energy deficit as defined by the ratio of reported average energy intake/calculated total daily energy expenditure (E/TDEE) and protein intake also did not significantly differ between those with short stature and those who were deemed to not have short stature (Table 3). Median MUAC z-score was lower in the short stature group, and the 4 patients with a MUAC z-score less than 2 standard deviations below the mean for age all had short stature (Table 3).

Growth hormone is a key determinant of linear growth in childhood and is released by the pituitary gland. Since the pituitary derives from ectodermal tissue and Wnt signaling is involved in pituitary formation, we performed a detailed examination of pituitary hormone function in our patients with FDH to see if *PORCN* mutation conferred a higher incidence of growth hormone deficiency. The pulsatile and highly regulated nature of growth hormone and cortisol release require stimulation tests to evaluate these hormonal axes. Glucagon administration provokes growth hormone and cortisol release in response to the fluctuations in serum blood glucose and therefore is commonly used in provocative testing for these hormones. Three of the 11 patients who underwent glucagon stimulation testing showed sub-standard growth hormone responses (peak GH levels of 4.08, 9.29 and 4.74 ng/ml, with >10 ng/ml considered a normal response). Two of these 3 patients with low GH responses had short stature, the other one appeared to be growing at her mid-parental height percentile (Table 1). One of these patients also failed to mount an appropriate cortisol response, suggesting multiple pituitary hormone deficiencies. No abnormalities were seen in thyroid hormone levels or electrolytes, suggesting that these other pituitary hormones (TSH, antidiuretic hormone) were normal. The one patient with a history of decreased growth velocity passed stimulation testing.

DISCUSSION

This study presents growth data on the largest group of children with FDH gathered thus far, as well as a preliminary examination of possible etiologies of short stature including nutritional factors, intercurrent disease and hormonal factors. Nearly 70% of the children had short stature (current height compared to parental heights and predicted final height), however less than 30% had low BMI ($<5^{\text{th}}$ percentile for age). Even though the lower body

fat percentage seen was statistically significant in FDH, it is important to note that it was still within the normal range for age. MUAC may be lower in those with short stature, which will need to be better elucidated in larger studies if possible given that our study group was small and no corrections were made for multiple comparisons in this pilot study. Screening for other common causes of growth failure such as celiac disease and inflammatory disease was negative. On average, dietary intakes were slightly less than recommended, however the overall normal BMI does not correlate with grossly inadequate intake, and fat intake was normal. Contrary to parental perceptions, our data suggest that undernutrition is not the major determinant of short stature in children with FDH. Children with FDH do not appear to be pre-disposed to a low BMI simply due to their genetic disease, therefore we recommend that nutrition should be optimized for those with a low BMI as standard pediatric care since adequate nutrition is necessary for optimal growth in all children.

We did not describe dental abnormalities in this population of patients. Could short stature be related to poor nutrition secondary to abnormal dentition? Wright and colleagues reported oral hard tissue anomalies in 94% and oral soft tissue anomalies in 68% of FDH patients they assessed (Wright, Puranik, & Farrington, 2016). However, patients with Hypohidrotic Ectodermal Dysplasia, the most common form of ectodermal dysplasia, have extensive dental anomalies and Motil et. al. found that mean height for age z scores were not significantly lower in this population, although mean weight for age z scores were significantly lower (Motil et al., 2005). Therefore, it is unlikely that dental anomalies causing undernutrition would account for short stature in FDH.

While Wnt signaling has been shown to play a role in ectodermal tissue development, our results do not clearly show that *PORCN* mutations cause pituitary hormone deficiencies despite the ectodermal origin of the pituitary gland. The suggestion of growth hormone deficiency in 3/11 patients is higher than expected, but certainly not universal. Given the paucity of data in whether *PORCN* determined Wnt signaling affects specific cell lines in the pituitary and the mosaic nature of the mutation, further studies will be needed to better elucidate the role of *PORCN* in pituitary development.

A limitation of the study is that we did not perform long bone radiographs to evaluate for skeletal dysplasia. Osteopathia striata has been described in a number of patients with FDH, but it is generally considered to be an incidental finding and has not been identified as a cause of short stature. Smith and Hunt reported reduction defects on long bones in 52.6% of 19 subjects in their orthopedic characterization of patients affected by FDH. These defects were largely unilateral and not speculated to be a cause of short stature (Smith & Hunt, 2016).

This study was a preliminary study performed to characterize growth in a rare genetic condition. As such, the small sample size limited the ability to perform meaningful multivariate analysis on the causes of growth failure in this group. In addition, the very young age of some of the patients and the pre-pubertal nature of most of the patients makes final height estimation more prone to error as unquantifiable pubertal variables will influence final height. There are also inherent inaccuracies in 3 day diet histories as they rely on patient report without verified observance (Natarajan et al., 2010) and the formulas used

to estimate energy expenditure may not accurately reflect the needs of the FDH population (Carpenter, Pencharz, & Mouzaki, 2015). While 3 patients had testing results suggestive of growth hormone deficiency, it is widely known that growth hormone stimulation testing is poorly reproducible and therefore current standard of care relies on the compilation of patient history, growth patterns, multiple stimulation tests, bone age radiographs and other studies to diagnose growth hormone deficiency (Stanley, 2012). In some cases, bone age determinations were more difficult due to hand abnormalities such as oligodactyly and ectrodactyly. Information on final height compared to parental heights in adult patients with FDH will better characterize the extent of short stature.

On a pragmatic note, in July 2003, the FDA approved the use of growth hormone for idiopathic short stature in children with a height more than 2.25 standard deviations below the mean. Studies showed that children with idiopathic short stature treated with 0.37 mg/kg/week of growth hormone obtained a height on average 2.8 inches above their predicted height at the start of treatment, with a 95% confidence interval of 1.8–3.9 inches (FDA, 2009; Frindik & Kemp, 2010). The rationale for this therapy is that current growth hormone testing only evaluates the generation and secretion of growth hormone in response to an artificial stimulus and that downstream defects are not tested but may be amenable to treatment. Clearly, not all children treated with growth hormone show an improvement in linear growth and many genetic syndromes and skeletal dysplasias are non-responsive to this therapy. Given our current information and results of this study, we do not recommend the routine use of growth hormone to treat short stature in FDH, but endorse an individual determination based on lab results and clinical characteristics.

Given the rarity of FDH, a global repository of clinical information would greatly enhance the characterization of this condition and guide the development of treatment recommendations. Our data is a first step in this process and suggests that the etiology of the growth failure in FDH may be multifactorial.

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Figure 1.

Growth failure in FDH patients. Individual height percentile vs. mid-parental height percentile. Gray circles highlight those patients who had suboptimal results to growth hormone stimulation testing.

Growth and hormonal data for study participants. GH, growth hormone; Ht, height; Wt, weight, BMI, body mass index; MPH, mid-parental height; Stim, stimulation test

Table 1.

Patient #	Age (y)	Sex	Wt %ile (z score)	Ht %ile (z score)	BMI %ile (z score)	MPH %ile	Bone Age ^a	Bone Abnor-malities	Puberty Stage ^b	Short Stature	GH Stim	Peak GH (ng/ml)	Cortisol Stim	Peak Cortisol (mcg/dl)
1	9.3	F	2.9 (-1.9)	0.7 (-2.4)	30.4 (0)	25-50	D	N	1	Y	Pass	11.3	Pass	29
2	14.5	F	63.6 (0.4)	56.0 (0.2)	62.4(0.3)	90-95	N	N	5	N	Pass	22.3	Pass	19
3	8.2	F	9.6 (-1.5)	1.3 (-2.2)	37.5 (-0.3)	75-90	D	Y	1	Y	-	-	-	-
4	9.3	M	43.6 (-0.2)	50.6 (0.0)	37.3 (-0.3)	90-95	N	N	1	N	Pass	10.6	Pass	22
5	7.5	F	1.8 (-2.1)	5.3 (-1.6)	5.0 (-1.6)	90-95	N	Y	1	Y	Fail	6.0	Pass	25
6	3.6	M	<0.1 (-4.3)	2.3 (-2.0)	<0.1 (<-4.2)	50-75	N	Y	1	Y	Pass	21.2	Pass	24
7	14.8	F	<0.1 (-4.3)	<0.1 (-4.3)	16.6 (-1)	20-50	A	Y	5	Y	-	-	-	-
8	17.6	F	0.2 (-3.1)	0.7 (-2.5)	0.1 (-2.6)	10-25	N	Y	5	Y	Pass	15.5	Pass	21
9	13.8	F	25.2 (-0.7)	1.9 (-2.1)	73.0 (0.6)	25-50	N	N	5	Y	Fail	9.3	Fail	9
10	7.3	F	6.4 (-1.5)	2.3 (-2.0)	34.8 (-0.4)	10-25	N	N	1	N	-	-	-	-
11	11.5	F	1.6 (-2.2)	0.9 (-2.4)	22.2 (-0.8)	25-50	A	Y	3	Y	-	-	-	-
12	5.9	F	30.7 (-0.5)	60.6 (0.3)	14.7 (-1)	50-75	N	N	1	N	Pass	13.7	Pass	23
13	10.1	F	10.1 (-1.3)	2.8 (-1.9)	46.8 (-0.1)	75-90	N	Y	1	Y	-	-	-	-
14	15.6	F	0.5 (-2.6)	0.03 (-3.4)	37.0 (-0.3)	50-75	A	N	5	Y	Pass	13.0	Pass	18
15	3.1	F	0.1 (-3.6)	9.9 (-1.3)	<0.1 (-4.2)	10-25	N	N	1	N	Fail	5.8	Pass	18
16	5.8	F	<0.1 (-4.2)	2.1 (-2.0)	<0.1 (<-4.2)	10-25	N	Y	1	Y	Pass	23.8	Pass	26
Median	9.3		2.3	2.2	26.3							13.0		22

^a A=advanced, N=normal, D=delayed

^b Puberty based on Tanner stage of genitalia (breasts, testes)

Summary of Nutritional Data. MUAC, Mid-upper arm circumference; E/TDEE, Calories consumed as a proportion of estimated total daily energy expenditure – values <1 suggest calorie deficit. Protein and vitamin D intake reported as a percentage of the Recommended Daily Allowance

Table 2.

Patient #	Age (y)	Sex	Short Stature	BMI %ile (z score)	Supplemental formula	MUAC cm (z score)	E/TDEE	Diet Analysis		Serum 25-OH Vitamin D (goal >30 ng/ml)
1	9.3	F	Y	30.4 (0)	Y	20 (-0.67)	0.9	182	127	62
2	14.5	F	N	62.4 (0.3)	N	25.2 (-0.49)	0.86	161	5	19
3	8.2	F	Y	37.5 (-0.3)	N	17.8 (-1.2)	1.28	447	49	
4	9.3	M	N	37.3 (-0.3)	N	20.6 (-0.37)	1.13	148	18	35
5	7.5	F	Y	5.0 (-1.6)	N	18.5 (-0.64)	0.93	174	6	26
6	3.6	M	Y	<0.1 (<-4.2)	Y	14 (-2.7)	0.68	158	7	35
7	14.8	F	Y	16.6 (-1)	N	18.9 (-3.0)	0.62	107	45	
8	17.6	F	Y	0.1 (-2.6)	N	18.5 (-3.7)	0.76	128	9	32
9	13.8	F	Y	73.0 (0.6)	N	23.1 (-0.55)	0.79	121	11	24
10	7.3	F	N	34.8 (-0.4)	N	18.4 (-0.62)				
11	11.5	F	Y	22.2 (-0.8)	N	20.8 (-1.1)				
12	5.9	F	N	14.7 (-1)	Y	17 (-0.8)	1.02	284	30	28
13	10.1	F	Y	46.8 (-0.1)	N	15 (-3.3)				
14	15.6	F	Y	37.0 (-0.3)	N	23.5 (-1.1)				11
15	3.1	F	N	<0.1 (-4.2)	Y	15 (-1.2)	0.41	185	15	33
16	5.8	F	Y	<0.1 (<-4.2)	Y	16.7 (-0.90)	0.68	116	9	30
Median	9.3			26.3		18.5 (-1.0)	0.82	143	13	30

Table 3.

Analysis of correlation between Short Stature in FDH patients and examined factors including growth hormone surrogates IGF-1 and IGF-BP3, body mass index (BMI), mid-upper arm circumference (MUAC) and dietary intake. E/TDEE: energy intake/estimated total daily energy expenditure; Protein(%RDA): protein intake as percentage of RDA (recommended dietary allowance). Values are reported as Median (25th percentile, 75th percentile) for the data set.

	Short stature		p-value
	Yes	No	
IGF-1 z-score (25,75 th %ile) N patients	0.027 (−0.030, 0.151) 7	0.047 (−0.016, 0.092) 4	0.79
IGF-BP3 z-score (25,75 th %ile) N patients	−0.002 (−0.03, 0.026) 7	0.026 (0.024, 0.041) 4	0.07
BMI %ile (25,75 th %ile) N patients	22.1 (0.07, 37.5) 11	32.3 (14.7, 34.8) 5	0.91
MUAC z-score (25,75 th %ile) N patients	−1.1 (−3.0, −0.67) 11	−0.62 (−0.80, −0.49) 5	0.047
E/TDEE (25,75 th %ile) N patients	0.78 (0.68, 0.92) 8	0.94 (0.64, 1.08) 4	0.65
Protein %RDA (25,75 th %ile) N patients	124 (111, 178) 8	173 (155, 235) 4	0.21