ARTICLE

Growth, Nutritional, and Gastrointestinal Aspects of Focal Dermal Hypoplasia (Goltz–Gorlin Syndrome)

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Focal dermal hypoplasia (FDH) is a rare genetic disorder caused by mutations in the *PORCN* gene located on the X-chromosome. In the present study, we characterized the pattern of growth, body composition, and the nutritional and gastrointestinal aspects of children and adults (n = 19) affected with this disorder using clinical anthropometry and a survey questionnaire. The mean birth length ($P < 0.06$) and weight ($P < 0.001$) z-scores of the participants were lower than the reference population. The mean head circumference ($P < 0.001$), height (length) ($P < 0.001$), weight ($P < 0.01$), and BMI ($P < 0.05$) for age z-scores of the participants were lower than the reference population. The height-for-age and weight-for-age z-scores of the participants did not differ significantly between birth and current measurements. Three-fourths of the group reported having one or more nutritional or gastrointestinal problems including short stature (65%), underweight (77%), oral motor dysfunction (41%), gastroesophageal reflux (24%), gastroparesis (35%), and constipation (35%). These observations provide novel clinical information about growth, body composition, and nutritional and gastrointestinal aspects of children and adults with FDH and underscore the importance of careful observation and early clinical intervention in the care of individuals affected with this disorder.

KEY WORDS: growth; body height; body weight; anthropometry; body fat; ectodermal dysplasia; short stature; malnutrition; gastroesophageal reflux; gastroparesis; constipation; gastrostomy

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INTRODUCTION

Focal dermal hypoplasia (FDH), also known as Goltz–Gorlin syndrome, is a rare genetic disorder that belongs to a heterogeneous group of the ectodermal dysplasias. The disorder is caused by a mutation in the *PORCN* gene located on the X-chromosome which gives rise to a variable range of phenotypes affecting skin, hair, teeth, and ocular and limb formation [Grzeschik et al., 2007; Wang et al., 2007]. The manifestations of FDH are variable and include skin and nail changes, eye anomalies, hand and foot abnormalities, facial dysmorphism, and abdominal wall defects.

Growth abnormalities have been described in children with several ectodermal dysplasia syndromes, including one child with FDH [Motil et al., 2005]. However, the patterns of growth and body composition and the nutritional and gastrointestinal aspects of this rare genetic disorder have not been characterized fully. Because of the paucity of information, the National Foundation for the Ectodermal Dysplasias (NFED) convened a workshop conference at Texas Children's Hospital and Baylor College of Medicine, Houston, TX, in March, 2013, to review the recent progress in basic and clinical research that has been made in this rare genetic disorder and to consider future research directions. Findings from that conference related to the patterns of growth, body composition, and the

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nutritional and gastrointestinal function in FDH are summarized in this article.

METHODS

Participants

All children and adults in attendance at the workshop conference 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 sample included 19 individuals, 17 females and 2 males. The median age of the participants was 9.0 years; the age range was 1–55 years. The racial distribution was characterized as 84% Caucasian (n = 16), one African-American, one Hispanic, and one bi-racial child.

The diagnosis of FDH was based on review of medical records and clinical evaluation by physician members of the NFED Scientific Advisory Committee.

The Institutional Review Board for Human Subject Research at Baylor College of Medicine approved the research study. Written, informed consent was obtained from the parents of all children younger than 18 years of age and directly from all individuals 18 years of age or older.

Procedures

Individual heights, weights, head and arm circumferences, and triceps, biceps, subscapular, and suprailiac skinfold thickness were obtained by direct measurement at the time of examination. Standing height measurements, without shoes, were obtained on children 2 years of age or older and were recorded to the nearest 0.1 cm. Length measurements, reclining without shoes, were obtained on children younger than 2 years of age and were recorded to the nearest 0.5 cm. Weight measurements were obtained using an electronic scale; values were recorded to the nearest 0.1 kg. Heavy clothes and shoes were removed before weighing. Body mass index (BMI) was calculated as the ratio of weight divided by height squared (kg/m^2) for children 2 years of age or older. Birth length and weight were ascertained from parental recall or available medical records. Z-scores for birth length and weight, height (length)-for-age, weight-for-age, and BMI-for-age were calculated from reference growth standards for the United States population established by the National Center for Health Statistics and the Centers for Disease Control and Prevention [National Center for Health Statistics, 2000]. Z-scores for adult individuals were assumed to be equivalent to those at age 20 years. Head circumference was measured from the glabella to the maximal occipital protuberance using a non-stretchable tape and converted to z-score values based on age- and gender-appropriate reference data [Nellhaus, 1968]. Arm circumference was measured at a point mid-way between the tip of the acromion and olecranon processes using a non-stretchable tape. The triceps, biceps, subscapular, and suprailiac skinfold thickness was measured with a skinfold caliper (Lange, Cambridge Scientific Industries, Inc., Cambridge, MD) using standard anthropometric techniques [Motil et al., 2006]. Arm muscle area was calculated from arm circumference and triceps skinfold measurements [Frisancho, 1981]. Arm muscle area and triceps skinfold thickness percentiles were calculated based on age- and gender-appropriate reference data from the National Health and Nutrition Examination Surveys [Frisancho, 1981]. Body fat, expressed as a proportion of body weight, was calculated from the triceps, biceps, subscapular, and suprailiac skinfold thickness measurements [Durnin and Rahaman, 1967].

A survey questionnaire that contained questions about growth and nutritional and gastrointestinal symptoms and diagnoses that reflected parental concerns was distributed to each participant or parent. The questionnaire included items related to age, estimates of height and weight; clinical symptoms and diagnoses related to common gastrointestinal and nutritional complaints; diagnostic procedures performed in response to symptoms; and nutritional interventions for each individual. The questionnaire was designed such that the parent or participant provided a "yes," "no," or "do not know" response to all categorical questions (symptom/diagnosis present or absent, procedures performed or not performed, intervention applied or not applied).

Data Analysis

Statistical analysis was performed using MiniTab statistical software (Version 13.0; MiniTab, Inc., State College, PA). Descriptive statistics (mean ± SD) were used to characterize the growth and anthropometric measures. One-sample *t*-tests were applied to detect differences ($P < 0.05$) in the mean birth length and weight [National Center for Health Statistics, 2000], head circumference-for-age [Nellhaus, 1968], height (length)-for-age, weight-for-age, and BMI-for-age [National Center for Health Statistics, 2000] z-scores and the mean arm muscle area and triceps skinfold thickness percentiles [Frisancho, 1981] between the participants and reference populations. Paired *t*-tests were used to detect differences in the mean height (length)-for-age and weight-for-age z-scores between birth and conference measurements. Descriptive statistics were used to determine the sample proportions for individual nutritional and gastrointestinal problems identified.

RESULTS

Measures of growth and body composition of the participants are shown in Table I. The mean birth weight z-score of the participants was lower ($P < 0.001$) than that of the reference population; the mean birth length z-score of the participants tended to be lower

TABLE I. Measures of Growth and Body Composition in Children and Adults With Focal Dermal Hypoplasia

Measure	Number of subjects	Value[a]
Birth length (cm)	14	46.0 ± 5.1
(z-score)	14	-2.0 ± 3.6
Birth weight (kg)	17	2.73 ± 0.61
(z-score)	17	-1.3 ± 1.1[b]
Head circumference (cm)	19	47.9 ± 3.9
(z-score)	19	-2.3 ± 1.0[b]
Height (cm)	19	122.6 ± 28.9
(z-score)	19	-1.0 ± 1.1[b]
Weight (kg)	19	31.5 ± 27.2
(z-score)	19	-1.3 ± 1.7[c]
Body mass index (kg/m^2)	17	18.1 ± 7.1
(z-score)	17	-0.9 ± 1.7[d]
Arm circumference (cm)	16	20.5 ± 7.1
Arm muscle area (mm^2)	16	2611 ± 1999
(percentile)	16	51 ± 32
Triceps skinfold thickness (mm)	19	11 ± 5
(percentile)	19	31 ± 25[d]
Biceps skinfold thickness (mm)	19	6 ± 4
Subscapular skinfold thickness (mm)	19	10 ± 9
Suprailiac skinfold thickness (mm)	19	9 ± 7
Body fat (% body weight)	19	22 ± 7

[a]Values expressed as mean ± SD.
[b]$P < 0.001$.
[c]$P < 0.01$.
[d]$P < 0.05$.

($P < 0.06$) than the reference population, but the difference did not achieve statistical significance. The mean head circumference-for-age ($P < 0.001$), height-for-age ($P < 0.001$), weight-for-age ($P < 0.01$), and BMI-for-age ($P < 0.05$) z-scores of the participants were lower than those of the reference population. The change in the mean weight-for-age (n = 16, 0.1 ± 1.3, NS) and height (length)-for-age (n = 13, -1.2 ± 3.1, NS) z-scores of the participants did not differ significantly between birth and current conference measurements. The mean triceps skinfold thickness ($P < 0.05$), but not arm muscle area, percentile of the participants was lower than that of the reference population. Body fat as a proportion of body weight averaged $22 \pm 7\%$ in the participants.

The nutritional and gastrointestinal concerns of the participants are summarized in Table II. Short stature and weight problems, primarily underweight, were reported in 65% and 77%, respectively, of the participants. Chewing problems and prolonged feeding times greater than 30 min were reported in 41% and 47%, respectively. Choking and swallowing difficulties were reported in 18%. Swallow function studies were obtained in 24% of participants. Food allergies, primarily milk, soy, and shellfish, were reported in 12% of participants. Multivitamin supplements were consumed by approximately one-half of the participants; formula supplements and herbal products were consumed by a minority. Gastrostomy placement with a fundoplication was performed in one participant. Gastroesophageal reflux and gastroparesis were reported in 24% and 35%, respectively, of participants. None had biliary tract disease. Gastrointestinal studies, including UGI series (18%), gastric emptying scans (18%), upper endoscopies (18%), and abdominal ultrasounds (29%) were obtained in a smaller proportion of these participants. Abdominal bloating (12%) and aerophagia (18%) were reported in a minority. Constipation was reported in 35% of participants. None reported gastrointestinal anomalies.

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DISCUSSION

Here, we have shown that height and weight deficits presented at an early age and persisted throughout childhood in children with FDH. Parental concerns, including short stature, underweight, oral motor dysfunction, gastroesophageal reflux, gastroparesis, or constipation, were noted. These observations provide novel information about the patterns of growth, body composition, and the nutritional and gastrointestinal aspects of children and adults with FDH and underscore the importance of careful observation and early clinical intervention in the care of children affected with this disorder.

Growth abnormalities commonly occur in children affected with the ectodermal dysplasia syndromes [Motil et al., 2005]. As a group, weight deficits of children affected with an ectodermal dysplasia occur at an early age and deviate significantly from the growth pattern of healthy children [Motil et al., 2005]. In contrast, height deficits occur predominately in children affected with ectodermal dysplasia syndromes other than hypohidrotic

TABLE II. Nutritional and Gastrointestinal Features of Children and Adults With Focal Dermal Hypoplasia

Finding	Number of "yes" responses	Proportion (%) with symptoms
Short stature	11/17	65
Nutritional status		
Underweight	11/17	65
Overweight	2/17	12
Food allergies	2/17	12
Chewing problems	7/17	41
Feeding time >30 min	8/17	47
Swallow difficulty	3/17	18
Choking	3/17	18
Nutritional supplements		
Formulas	3/17	18
Multivitamins	9/17	53
Herbals	2/17	12
Gastrostomy/ fundoplication	1/17	6
Gastroesophageal reflux	4/17	24
Gastroparesis	6/17	35
Biliary tract disease	0/17	0
Abdominal bloating	2/17	12
Aerophagia	3/17	18
Constipation	6/17	35

ectodermal dysplasia [Motil et al., 2005]. In the present study, weight and height deficits of children affected with FDH were present at an early age and persisted throughout childhood. Improvement in weight deficits with advancing age was not apparent in children with FDH, a pattern that differs from children with hypohidrotic ectodermal dysplasia [Motil et al., 2005]. In addition, the smaller head size of the participants affected with FDH paralleled the smaller body size compared with the reference data [Nellhaus, 1968]. Clinical anthropometry provided a crude estimate of mildly decreased body fat in the participants with FDH, a pattern that differed from children with the ankyloblepharon-ectodermal defect-cleft lip and/or palate (AEC) syndrome [Motil and Fete, 2009]. The factors that account for altered growth and body composition in individuals with FDH are unknown, but presumably have a multifactorial genetic, nutritional, and gastrointestinal basis.

In the present study, weight and height deficits of children affected with FDH were present at an early age and persisted throughout childhood. Improvement in weight deficits with advancing age was not apparent in children with FDH, a pattern that differs from children with hypohidrotic ectodermal dysplasia.

Gastrointestinal issues have been described rarely in the ectodermal dysplasia syndromes [Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias, 1995; Motil and Fete, 2009]. A previous survey conducted by the NFED suggested that individuals with hypohidrotic ectodermal dysplasia may have constipation more frequently than unaffected individuals; a small number was diagnosed with gastroesophageal reflux and failure to thrive rarely requiring a feeding gastrostomy [Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias, 1995]. In a more recent survey conducted by the NFED, one-fourth of children with the AEC syndrome reported the need for supplemental formula feedings, gastrostomy placement, or treatment for gastroesophageal reflux and constipation [Motil and Fete, 2009]. In the present study, oral motor and swallowing dysfunction was documented in nearly one-half of the individuals with FDH, a factor that presumably contributed to the weight and body fat deficits in individuals affected with this disorder. We noted that few individuals received nutritional interventions to address the weight deficits. Food allergies were nearly 50% less frequent in the participants with FDH compared with a much larger cohort of individuals with a broad spectrum of the ectodermal dysplasias [Mark et al., 2012]. The factors that account for these differences are unknown, but suggest that the genetic basis for the spectrum of ectodermal dysplasias is quite broad. Approximately, one-fourth to one-third of the participants with FDH had problems related to gastrointestinal motility including gastroesophageal reflux, gastroparesis, or constipation. Similar complaints were reported by parents of children with the AEC syndrome, although the prevalence of gastroesosphageal reflux was nearly twofold greater in the latter group [Motil and Fete, 2009]. Gastrointestinal anomalies, including diaphragmatic hernia, omphalocoele, umbilical hernia, ectopia cordis, and malrotation have been reported in a small number of children with FDH [Patel et al., 1997; Han et al., 2000; Riyaz et al., 2005; Maas et al., 2009; Smigiel et al., 2011]. Abdominal wall defects were not identified in the present group of children.

In summary, children and adults with FDH have clinical evidence of

growth abnormalities and nutritional and gastrointestinal problems. Careful clinical assessment and appropriate therapeutic interventions are warranted to optimize the quality of life of individuals affected with this disorder.

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