Growth Charts for Individuals With Rhizomelic Chondrodysplasia Punctata

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Rhizomelic chondrodysplasia punctata (RCDP) is a class of peroxisomal disorders characterized by defective plasmalogen biosynthesis. There are multiple recognized types of RCDP, all of which have autosomal recessive inheritance, and their associated genes are known: RCDP type 1 with PEX7, RCDP type 2 with GNPAT, RCDP type 3 with AGPS, RCDP type 4 with FAR1, and RCDP type 5 with PEX5. Among other medical/developmental issues, plasmalogen deficiency has a direct effect on bone growth and results in postnatal growth failure, the severity of which corresponds to the degree of plasmalogen deficiency. In order to document growth in patients with RCDP, we present detailed growth curves for length, weight, and head circumference derived from retrospective data from 23 individuals with RCDP types 1 and 2 confirmed by molecular and/or biochemical studies. We stratified growth curves by age as well as by plasmalogen level, with those with higher plasmalogens grouped as “non-classic.” The growth charts presented here provide guidance to families and physician caretakers on the natural course of growth in individuals with RCDP during infancy into early childhood, and thus will have particular utility in setting expectations and guiding optimal feeding interventions in this population.

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INTRODUCTION

Rhizomelic chondrodysplasia punctata (RCDP) is a class of peroxisomal disorders characterized by defective plasmalogen biosynthesis [Braverman and Moser, 2012]. There are three well-recognized types of RCDP: types 1, 2, and 3. For each, a causative gene has been identified: PEX7 with RCDP type 1 [Braverman et al., 1997; Motley et al., 1997; Purdue et al., 1997], GNATP with RCDP type 2 [Ofman et al., 1998; Itzkovitz et al., 2012], and AGPS with RCDP type 3 [de Vet et al., 1998; Itzkovitz et al., 2012]. In RCDP type 1, the most common type, plasmalogen deficiency results from the inability of a defective PEX7 protein to bind and transport the AGPS enzyme from the cytosol to the peroxisome. In RCDP types 2 and 3, the defect is isolated to the two peroxisomal enzymes required to initiate plasmalogen synthesis, AGPS and GNPAT respectively. Recently, RCDP type 4 has been described due to defects in FAR1, which encodes the enzyme that generates the fatty alcohol substrate for AGPS [Buchert et al., 2014; Wanders and Poll-The, 2015]. Additionally, RCDP type 5 has been described in which a specific mutation in PEX5 abolishes its ability to bind PEX7 [Barøy et al., 2015]. The phenotypes thus far of RCDP1, 2, 3, and 5 are indistinguishable; RCDP 4 patients also show growth impairment.

Overall, RCDP has an estimated incidence of approximately one in 100,000 live births [Stoll et al., 1989]. The diagnosis is confirmed by appropriate biochemical and/or molecular genetic testing. Those individuals with the classic RCDP phenotype that survive infancy have profound cognitive impairment and physical disabilities [Spranger et al., 1971; Wardinsky et al., 1990; White et al., 2003].

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but individuals with less severe plasmalogen deficiency have been reported with less severe growth and neurologic involvement [Braverman et al., 2002; Bams-Mengerink et al., 2013], supporting a relationship between residual plasmalogen levels and phenotype.

Orthopedic manifestations of RCDP include shortened proximal limbs, a stippled appearance to the epiphysial cartilage, contractures with stiff/painful joints, cervical stenosis, and kyphoscoliosis. A majority of individuals have cataracts detected at birth or in infancy. Many also have congenital heart defects [Huffnagel et al., 2013; Duker et al., 2016]. Weight, length, and head circumference are often at the lower range of normal at birth, but postnatal growth deficiency is profound. [Spranger et al., 1971; Wardinsky et al., 1990; White et al., 2003].

As poor growth is the norm for children with RCDP, condition-specific growth curves are an important tool to aid in the medical management of children with this disorder. To date, the only published growth estimates for RCDP are a best-fit line for length as well as weight for individuals under 3 years of age [White et al., 2003]. Here, we present the first detailed growth curves for height, weight, and head circumference for individuals with this condition, from infancy to 12 years of age. Also, given the dramatically slow weight gain in this population, we also include expected weight for length growth grids as well as grids of expected daily weight gain by age, to help focus expectations for care providers. Additionally, as some individuals with RCDP have been described as having a mild phenotype (i.e., “non-classic”) due to a mild/moderate plasmalogen deficiency, we provide growth curves both for classic and non-classic RCDP.

METHODS

Patient Population

To systematically ascertain the medical problems associated with RCDP, an Institutional Review Board-approved Rhizomelic Chondrodysplasia Punctata Registry was created at Nemours/Alfred I. duPont Hospital for Children. This international registry collects retrospective medical records and will continue to do so over time, to more robustly identify pertinent issues over the lifespan of individuals with RCDP. To date, 23 individuals with RCDP types 1 and 2 have been enrolled via an informed consent process. All have had appropriate biochemical and/or molecular confirmation of their clinical diagnosis of RCDP (see Supplemental Table SI).

“Classic” was differentiated from “non-classic” RCDP by using the cut-off of their plasmalogen levels. Specifically, non-classic was anyone with results ≥0.05 for C18:0 DMA/C18:0 fatty acid, and classic was anyone with results <0.05 for C18:0 DMA/C18:0 fatty acid, with the typical “classic” levels of 0.001 being 50-fold less than “non-classic.” Two patients molecularly confirmed with RCDP type 1 but without plasmalogen level results in our registry were labeled as “classic” for these purposes, given their common genotype predicting null mutations.

Growth Chart Calculation

Data were modeled using the R statistical language [R Core Team, 2014] and regression analysis. The longitudinal nature of the data dictated the use of random effects models to account for the inter-subject variability. However, the models also had to represent physical reality and increase monotonically, a feature that was not always possible without treating all data points as being independent. Therefore, both fixed and random effects models were fit to the data and compared based on Akaike Information Criterion (AIC) [Saefken et al., 2014]. Models with the lowest AIC were chosen so long as the trends were monotonically increasing. For a given estimate of weight, height, or head circumference (Y) for the ith subject at time, t, the random effects models were specified as:

\[ Y_{it} = A \log (t_i + B) + C \sqrt{t_i} + D + u_i + e_{it} \]  

where A, B, C, and D are constants fit by the regression, \( u_i \) accounted for the between subject error, and \( e_{it} \) accounted for the within subject error. The fixed effects model differed in that the individual data points were considered to be independent and therefore equally weighted.

\[ Y_{t} = A \log (t + B) + C \sqrt{t} + D + u \]  

where in this case, \( u \) represents the error term.

The superposition of logarithmic and square-root functions instead of spline models or local regression were chosen to represent the data to attempt to model a population trend. Data were modeled from ages 0–36 months and from 2 to 12 years. Resultant models were plotted both with and without data.

Height–weight curves were fit to classic and non-classic populations using least squares with a quadratic function

\[ W_t = A H_t^2 + B + u \]  

where \( W_t \) is the weight of an individual at time t (age), \( H_t \) is the corresponding age, A and B are coefficients of fit, and u is the error term.

Expected weight change curves obtained by taking the slope of the fitted weight versus age curves for each group and converting y-axis units to grams per day.

RESULTS

Patient Characteristics

In total, we studied 12 males and 11 females with a molecularly and/or biochemically confirmed diagnosis of RCDP, ranging in age at time of final data collection from 1 to 13 years. “Non-classic” data points were ascertained from two males and two females, two of which were siblings with RCDP type 2. “Classic” phenotype includes one individual with RCDP type 2 and the remainder with RCDP type 1. The total number of data points collected for length was 197, for weight was 359, and for head circumference was 167. When known, measurements of length following along segments were excluded from the analysis, as these were identified as overall outliers given the increased length noted, and due to a majority of the measurements presumed crown to heel.

Growth Curves for RCDP

Combined charts for males and females for length/height (Figs. 1 and 2), weight (Figs. 3 and 4), and head circumference (Figs. 5 and 6)
were created, stratified by “classic” and “non-classic,” with separate grids for infants less than 36 months and children greater than 3 years of age. The Center for Disease Control (CDC) growth charts for boys [Kuczmarski et al., 2000] with the 5th, 50th, and 95th centiles are superimposed for comparison on all of these curves, with the exception of the head circumference grid over the age of two, for which the Rollins et al. [2010] head growth grid for males was used. See Supplemental Figures S1–S12 for grids which are the same as above but without data points included, and with separate grids for classic and non-classic to limit unnecessary lines for ease and practicality of use in clinic. A weight for height chart was also constructed for classic (Fig. 7) and non-classic (Fig. 8). Additionally, rate of weight change grids for those under 12 months as well as those over a year of age was compiled (Figs. 9 and 10).

Random effects models fit the data most consistently except for the weight and head circumference of older classic RCDP patients where fixed effects models were used. In the case of weight, the fixed effect model was a better fit. In the case of head circumference, the

**FIG. 1.** Length for age for children with RCDP <3 years old. CDC boys length for age is superimposed. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid 0.05.

**FIG. 2.** Length for age for children with RCDP between 3 years and 12 years old. CDC boys length for age is superimposed. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid 0.05.

**FIG. 3.** Weight for age for children with RCDP <3 years old. CDC boys weight for age is superimposed. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid 0.05.

**FIG. 4.** Weight for age for children with RCDP between 3 years and 12 years old. CDC boys weight for age is superimposed. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid 0.05.
fixed effect model showed constant head circumference with increasing age rather than an artificially decreasing head circumference.

**DISCUSSION**

Marked growth failure was evident throughout the lifespan for all children with RCDP, with children with higher plasmalogen levels demonstrating better growth compared to the classic RCDP phenotype. We believe that the cohort of patients which have been consented into the registry, and whose data are used to generate these curves, are representative of the overall RCDP population. While management of these complex children can be difficult, we expect that the spectrum of growth possibilities which can be seen are reflected in the data and hence the curves. The fact that overall growth differences are seen in patients with different plasmalogen levels suggests that we are able to represent intrinsic growth patterns in the curves.

Regarding head circumference growth, though there were some non-classic data points within two standard deviations of the typical range, individuals with classic RCDP were universally microcephalic, with effectively no head circumference growth after 3 years of age (Fig. 6).

In general, for individuals with classic RCDP, length is difficult to measure given contractures of the lower extremities as well as...
kyphoscoliosis. Also, many older children were measured supine instead of true height, given they were non-ambulatory. For some individuals in this study, lengths were performed by one of the authors (NHB) tracking along the segments of contractures (data not included in the construction of the growth curves), and as much as 5–6 cm longer length was noted when compared to the child’s measurements from their primary care physician within the same month. Though the measurable lengths were affected by contractures and less than typical even without contractures, linear growth is still more robust than the weight gain (Fig. 2), which were the same findings as White et al. [2003].

Weight gain is a chronic issue for children with RCDP, and these charts graphically exhibit this. The difference between classic and non-classic is most apparent in the rate of weight change grids, which note expected daily weight gain is approximately double with plasmalogen levels of non-classic versus classic RCDP (Figs. 9 and 10). The weight for age grid for 3–12 year olds (Fig. 4) shows on average for classic RCDP, there is a lack of meaningful weight gain over any 12-month period in that timeframe, although some limited weight gain does occur. Figure 10 demonstrates that for those with classic RCDP, one should not expect more than 1–2 g per day of weight gain after 3 years of age. For infants with classic RCDP, expected weight gain dramatically drops after the first few months of life, down to 5 g per day by 6 months of age (Fig. 9).

It is our experience that one or any combination of poor weight gain in infancy, feeding intolerance, aspiration, and gastroesophageal reflux disease often leads to discussion of gastrostomy tube placement with or without Nissen fundoplication for infants with RCDP. In fact, 65% of the 23 individuals included here from the registry have a gastrostomy tube. However, knowing when this intervention is needed, as well as what type of formula to use, and how many calories to provide, in addition to weight gain expectations, have been questions without clear answers for local health care providers. We believe our growth curves can help provide assistance as to expectations for daily weight gain by age, as well as by proportions, and overall trend of growth over time.

Insofar as what type of nutrition to provide, it is important to remember that children with RCDP type 1 are unable to import into the peroxisome the PEX7-dependent enzyme needed for plasmalogen synthesis alkylidihydroxyacetonephosphate synthase (AGPS), as well as phytanoyl-CoA hydroxylase (PhyH), the enzyme involved in phytanic acid alpha-oxidation. Humans do not make but instead receive exogenous phytanic acid from the diet. Infant and pediatric formulas do not contain phytanic acid, but certain foods do. The accumulation of high levels of phytanic acid over time could lead to symptoms of adult Refsum disease (isolated PhyH deficiency), although this has not been reported with RCDP, either because phytanic acid levels never achieve the levels seen in adult Refsum disease because most children are mainly formula fed, or because these patients have not lived long enough to see this effect. Regardless, our recommendation is to lower phytanic acid intake in non-formula fed children with RCDP type 1. As individuals with RCDP types 2 and 3 have the ability to process phytanic acid, this intake reduction would not be necessary for them.

A typical diet will have from 50 mg to 100 mg per day of phytanic acid and this can be decreased to 10–30 mg/day by avoiding beef, lamb, game birds, fatty fish, and fish oil. The rationale is that rumen microorganisms convert phytol from the chlorophyll of grass to phytanic acid, and fatty fish feed on krill which also converts the green pigment of algae into phytanic acid. Phytanic acid is stored in ruminant animal milk, organs, and fat as well as fish. Fully breastfed infants consume up to 750 mL of breast milk a day. Dependent on the maternal diet, a fully breastfed child has a phytanic acid intake estimated in the range of 0.20–3.2 mg each day, which is within the restricted range [Brereton et al., 2003].

As noted above, 65% of children in our registry with RCDP are g-tube fed either with pumped breast milk or formula. Tolerated formulas appears to be equally selected between typical pediatric

![Rate of weight change for children with RCDP <12 months old. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid ≥0.05.](image)

![Rate of weight change for children with RCDP 1–12 years old. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid. Non-classic data are from children with a diagnosis of RCDP, but with C18:0 DMA/C18:0 fatty acid ≥0.05.](image)
formulas, and semi-elemental and elemental formulas. The nutrient density ranges from 0.63 calories to 1.2 calories per milliliter. Further study is needed to determine the precise caloric requirements of individuals in the classic and non-classic groups.

One may note that a weakness of this analysis is the small sample size. However, we posit that for this ultra-rare genetic condition with a limited lifespan, this is a substantial number of collected data points over a significant number of years. To account for the paucity of data points in the older ages, the standard error curves do widen. Previously, published length and weight grids for individuals with RCDP under the age of 3 years [White et al., 2003] included more individuals in their retrospective review. However, on comparison, there is a reasonable degree of similarity between their anticipated growth and our classic RCDP growth grids for that age range.

Overall, we believe the various growth curves provided will be paramount in assisting in the estimation of nutritional needs of a child with RCDP, by providing appropriate standards by which to base expectations of growth.

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REFERENCES


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