Received: 3 April 2017 | Revised: 7 July 2017 | Accepted: 10 August 2017
DOI: 10.1002/ajmg.a.38467

RESEARCH LETTER

WILEY AMERICAN JOURNAL OF medical genetics PART A

Expected weight gain for children with microcephalic osteodysplastic primordial dwarfism type II

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Funding information
Potentials Foundation; Walking with Giants Foundation

To the Editor:

Microcephalic osteodysplastic primordial dwarfism type II (MOPDII; OMIM #210720), first described by Majewski, Ranke, and Schinzel (1982), is the most common distinctive diagnostic entity within the group of microcephalic primordial dwarfism syndromes (Hall, Flora, Scott, Pauli, & Tanaka, 2004; Klingseisen & Jackson, 2011; Rauch, 2011). Aside from the classic features of severe pre- and post-natal growth failure together with microcephaly, individuals with MOPDII have a characteristic skeletal dysplasia (Hall et al., 2004; Willems et al., 2009) with a specific hip pathology (Karatas et al., 2014), abnormal dentition (Kantaputra et al., 2011), an increased risk for cerebrovascular disease (Bober et al., 2010; Brancati, Castori, Mingarelli, & Dallapiccola, 2005; Waldron et al., 2009), and insulin resistance (Huang-Doran et al., 2011). MOPDII has autosomal recessive inheritance and is caused by mutations in the pericentrin (*PCNT*) gene (Rauch et al., 2008).

Typically, infants born small for gestational age are fed aggressively in an attempt to improve growth (Hall et al., 2004). However, given the underlying nature of MOPDII, typical growth velocities are unattainable. It is our experience that many individuals with MOPDII have gastrostomy tubes recommended, if not placed, in the neonatal period, given their exceedingly slow weight gain.

In order to help guide management of the child with MOPDII, we previously published detailed growth curves for height, weight, and head circumference, as well as weight for height curves to assess proportions, for 26 individuals with MOPDII with PCNT mutations or demonstrated absence of PCNT protein (Bober et al., 2012). It has since become apparent that a valuable metric to help guide the nutritional management of an infant with MOPDII is having an appropriate expectation of weight gain per day by age. We recently generated this type of curve for a different dysplasia diagnosis, and it has proven quite helpful in the clinical setting (Duker et al., 2017).

To that end, we are including here the grams per day expectations from birth to 17 years for individuals with MOPDII, using the same ascertainment of patients published in Bober et al. (2012). To date, 32 patients in the Nemours IRB approved Primordial Dwarfism Registry have molecular confirmation of their MOPDII diagnosis as well as weight measurements for analysis.

Longitudinal weight data comprising 446 distinct datum from 32 patients (15 female, 17 male) ranging in age from birth to 28 years were analyzed. Data point count binned by year is noted in Supplemental Figure S1. All data utilized were from prior to the initiation of any growth hormone supplementation. Weight versus age data were resampled with replacement 100 times and fit using a locally weighted regression model (LOESS) with a span of 0.99 (Cleveland, Grosse, & Shyu, 1992). The derivative of this fit was calculated using a central difference method, and then re-smoothed using LOESS with a span of 0.90. Span parameters which dictated the degree of smoothing in the model were chosen to ensure monotonic increases or decreases in the data and smooth out local effects that might imply non-existent decreases in weight as age increased. The resultant weight-velocity curve was the mean of the bootstrapped curves surrounded by a band indicating the bootstrapped standard deviation. This was then plotted both from birth to 17 years. Because later data was from a single subject whose mean weight was below the group average, this caused an unrealistic down-turn in the weight versus age graph. All statistics were done using R statistical software (R Core Team, 2017).

As noted in Figure 1, and contrasting with a typical neonate, infants with MOPDII have an expected weight gain of approximately 2 g/d throughout their first year of life. As the figure continues to

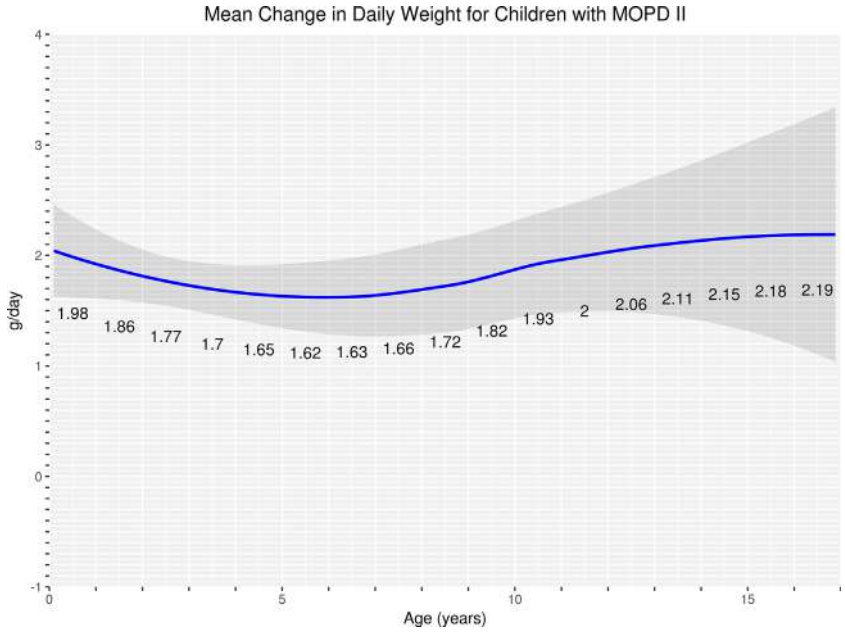

FIGURE 1 Average change in daily weight gain for males and females with MOPDII, from birth to 17 years of age, with average daily gain indicated directly per year. [Color figure can be viewed at wileyonlinelibrary.com]

demonstrate, the expected weight gain of a child with MOPDII hovers around two grams per day throughout their childhood. Though this is a dramatically different pattern when compared to a typical infant/child's weight gain, it should not be entirely unexpected given the underlying etiology of MOPDII, which is caused by loss of function of *pericentrin*. This leads to abnormal mitosis resulting in reduction in cell number and thus a rate-limiting step for growth (Klingseisen & Jackson, 2011).

Limitations to this study include our differing weight data points per age, with more points available in the first two years of life compared to older ages. However, as questions regarding the nutritional needs, and possible surgical management, of children with this diagnosis are more pressing in infancy, we feel this analysis is robust in the time frame in question. Empirically, we have noted truncal obesity start to develop in the teenage years, which could explain the identified uptick in expected grams/day in this age-range.

Overall, we are hopeful this average ~2 grams per day expectation, combined with our previously published typical growth curves, can optimize nutritional management of children with MOPDII.

ACKNOWLEDGMENTS

This work is supported in part by the Potentials Foundation, and the Walking with Giants Foundation. We thank all of the families who participate in the Primordial Registry at the Alfred I. duPont Hospital for Children. This work would not be possible without their contributions. We would like to thank Tara Ketterer and Grant Eldridge, who helped transfer growth points into the registry database, our dysplasia research coordinator Cassie Brown, and our collaborators who contributed to our previous analysis of growth in MOPDII: Louise Bicknell, Margaret Harley, Jennie Murray, Andrew Jackson, Christina Flora, Sabah Alvi, Cecilie Rustad, Ernie Bongers, and Carol Wise.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Duker AL, Niiler T, Bober MB. Expected weight gain for children with microcephalic osteodysplastic primordial dwarfism type II. *Am J Med Genet Part A*. 2017;173A:3067–3069.
https://doi.org/10.1002/ajmg.a.38467