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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Growth in Chilean Infants With Chromosome 22q11 Microdeletion Syndrome

Maria Luisa Guzman,[1] Iris Delgado,[2] Guillermo Lay-Son,[1,3,4] Edward Willans,[1,5] Alonso Puga,[1] and Gabriela M. Repetto[1,2,6]*

[1]Center for Human Genetics, Facultad de Medicina Clinica Alemana-Universidad del Desarrollo, Santiago, Chile

[2]Center for Epidemiology and Public Health Policy, Facultad de Medicina Clinica Alemana-Universidad del Desarrollo

[3]Unidad de Gestión Clínica del Niño, Hospital Padre Hurtado, Santiago, Chile

[4]Unidad de Genética, Hospital Luis Calvo Mackenna

[5]Department of Life Sciences, Imperial College, London, England

[6]Department of Pediatrics, Clinica Alemana, Santiago, Chile

Manuscript Received: 7 December 2011; Manuscript Accepted: 17 May 2012

Chromosome 22q11 microdeletion syndrome has a wide range of clinical manifestations including congenital heart malformations, palatal defects, endocrine abnormalities, immunologic deficits, learning difficulties, and an increased predisposition to psychiatric disease. Short stature and poor weight gain in infancy are common findings and are usually seen in the absence of hormone deficiencies. An increased frequency of obesity has been observed in adolescents and adults. We generated gender-specific growth curves from 0 to 24 months of age, based on 479 length and 475 weight measurements from 138 Chilean patients with 22q11 deletion. Final adult height and weight on 25 individuals were analyzed. The 10th, 50th, and 90th centile-smoothed curves for infants were built using the LMS method and compared with World Health Organization Child Growth Standards. The 50th centile for length in the deleted patients was slightly lower than the 10th centile of WHO standards in boys and girls. The same was observed for weight, although a trend toward a gradual increase near 2 years of age was observed, particularly in boys. Average adult height was 152 cm (ranging from 143 to 162 cm) in females, corresponding to the 10th centiles of WHO standards, and 166 cm for males (160–172 cm), at the 20th centile of WHO standards. A third of the adult females and none of the males had body mass index (BMI) greater than 25. The curves should be useful to monitor growth in infants with 22q11 microdeletion syndrome.

Key words: 22q11 deletion; congenital heart disease; DiGeorge syndrome; growth curves

How to Cite this Article:
Guzman ML, Delgado I, Lay-Son G, Willans E, Alonso P, Repetto GM. 2012. Growth in Chilean infants with chromosome 22q11 microdeletion syndrome.
Am J Med Genet Part A 158A:2682–2686.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (del22q11) or velocardiofacial syndrome (VCFS) is one the most common genomic alterations in humans, with an estimated frequency of 1/2,000 to 1/4,000 livebirths [Shprintzen, 2005]. Common manifestations include congenital heart defects, palate defects, immune deficits, hypocalcemia, learning difficulties, and increased risk of psychiatric disease [McDonald-McGinn et al., 1999; Shprintzen, 2008; Repetto et al., 2009; Bassett et al., 2011]. In addition, frequencies of short stature ranging from 10 to 60% in childhood have been described in several clinical series [Shprintzen et al., 1981; Lipson et al., 1991; Goldberg et al., 1993; Weinzimer et al., 1998; Digilio et al., 2001]. Individual cases of severe short stature have been attributed to growth or thyroid hormone deficiencies [Weinzimer et al., 1998; Weinzimer, 2001]. Nevertheless, slow growth is most frequently seen in patients with VCFS that do not have endocrine deficiencies, suggesting that short stature may be a primary manifestation of the syndrome or perhaps secondary to feeding difficulties in infancy due to pharyngeal hypotonia. Adolescent and final adult heights tend to be in the normal range, closer to the expected for mid-parental height. An increased frequency of obesity has also been described in school-age children, supporting the hypothesis that

Grant sponsor: Fondecyt-Chile grants; Grant numbers: 1061051, 1100131.
*Correspondence to:
Gabriela M. Repetto, MD, Center for Human Genetics, Facultad de Medicina, Clinica Alemana-Universidad del Desarrollo, Av Las Condes, 12438 Santiago 7710162, Chile. E-mail: grepetto@udd.cl
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 6 August 2012
DOI 10.1002/ajmg.a.35525

early feeding problems may be the cause of poor growth in infancy [Digilio et al., 2001; Shprintzen et al., 2008].

Growth curves for patients in the USA have been published [Shprintzen et al., 2008], but are unavailable for patients from other geographic or ethnic origins. We present length and weight growth curves on Chilean infants up to 2 years. We also describe height, weight and body mass index (BMI) for adults with VCFS.

METHODS

Patients with FISH-proven 22q11 microdeletion syndrome participated in the study. They were recruited from all centers that perform FISH testing in the country, as part of a study on the natural history of the syndrome. All cytogenetics laboratories in Chile use TUPLE1 probe (Abbott Laboratories, Abbott Park, IL) for diagnosis of the deletion. Retrospective data on weight and recumbent length from birth to 24 months of age, as well as final weight and standing height in patients 18 years or older were collected. Measurements were obtained according to standard techniques during routine pediatric visits in primary care clinics or genetics evaluation in tertiary centers, using balance beam scales, calibrated horizontal boards for infants and stadiometers for adults. Patients with a history of prematurity or with growth or thyroid hormone deficiencies were excluded from the study.

Gender-specific growth curves for ages 0–24 months were constructed by calculation of frequency distributions, determination of centiles for each of the anthropometric measurements, and estimation of the measures for central tendency and dispersion. To allow for comparisons, the growth curves for patients with the deletion were constructed with the same methodology as the published WHO growth standards for infants [World Health Organization, 2006, and 2009]. These curves are routinely used in Chile for pediatric growth assessment [Ministerio de Salud de Chile, 2007]. The LMS method was used to calculate the 10th, 50th, and 90th centile for length and weight for each gender [Cole and Green, 1992]. LMS refers to λ, μ, and σ, corresponding to the L curve (Box–Cox power to remove skewness), M curve (median), and S curve (coefficient of variation), respectively. Curves were smoothened using the Box–Cox-power exponential transformation method through cubic splines [Box and Cox, 1964].

The optimal power value of the transformation was estimated for each corresponding, gender-specific centile. Since centiles determined from a normal distribution are more precise, the LMS method determines a transformation such that the gender and age-specific measurements approach a normal distribution [Cole and Green, 1992; World Health Organization, 2009; Butler et al., 2011]. Statistical analysis was performed using software v.18.0 SPSS (IBM Corporation, Armonk, NY).

We collected final adult standing height and weight measurements obtained during genetics evaluations. BMI was calculated using these results.

The study was approved by the Institutional Review Board at all participating institutions and parents and/or patients gave written informed consent.

RESULTS

Birth weight and length information was available on 239 individuals with FISH-proven deletions, accounting for 68% of known patients in Chile at the time of data collection. One hundred and eighteen (49.4%) were females. Birth weight average (± 1 SD) was $3.08\,\text{kg} \pm 2.35$ (3.22 ± 0.47 for males and 2.92 ± 0.48 for females, $P < 0.05$) and birth length, 47.4 ± 3.4 cm (49.16 ± 2.73 for males and 47.8 ± 2.44 for females, $P < 0.05$).

One hundred and thirty eight patients (40% of known patients) had two or more anthropometric data from 0 to 24 months,

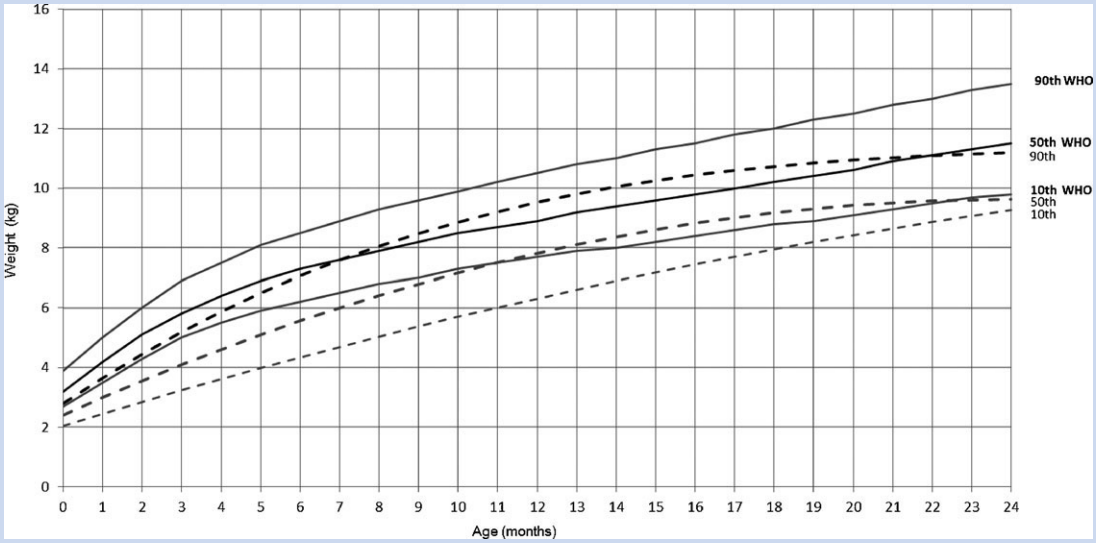

FIG. 1. Weight in girls from 0 to 24 months. Solid lines represent the 10th, 50th, and 90th centiles of WHO Growth Standards. Dotted lines represent the same centiles in girls with 22q11 microdeletion.

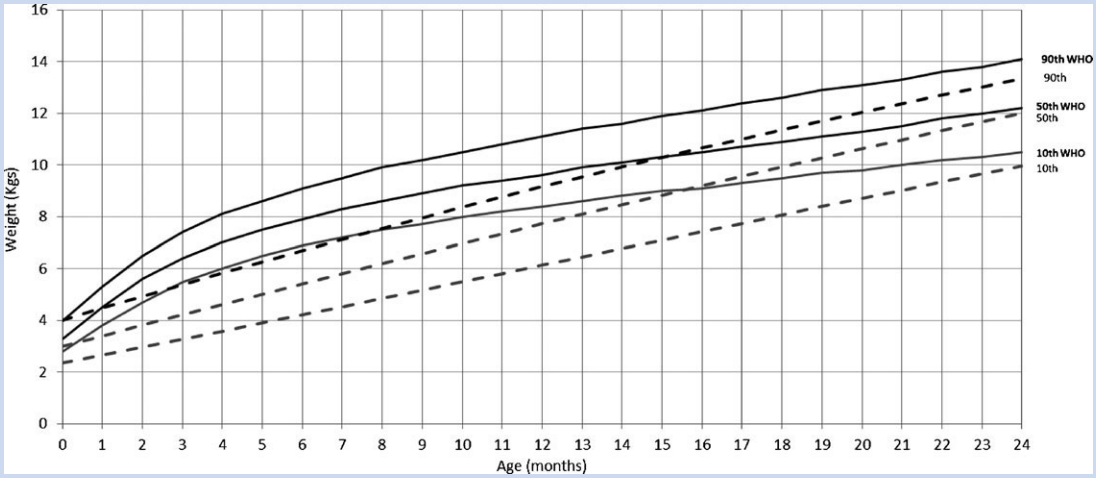

FIG. 2. Weight in boys from 0 to 24 months. Solid lines represent the 10th, 50th, and 90th centiles of WHO Growth Standards. Dotted lines represent the same centiles in boys with 22q11 microdeletion.

resulting in 479 length measurements and 475 for weight. This group was composed of 65 girls and 73 boys (47.1 and 52.9%, respectively). An average of 3.5 data points per patient, with a median of 3 and a range of 2–10 measurements were available. Data from 0–3 months of age comprised 23% of measurements; 4 –12 months of age, 47%, and 13–24 months, 30%. Congenital heart defects were present in 88 patients (64.2%).

Growth curves for boys and girls were constructed and compared with WHO standards (Figs. 1–4). Weight in infants younger than 6 months was below the 10th centile of WHO growth standards for the majority patients, but tended to increase gradually (Figs. 1 and 2). The latter trend was more evident in boys, whose weight centiles at 24 months were only slightly lower than their equivalent WHO standards. Regarding length, the 50th centile for boys and girls with 22q11deletion was below the WHO 10th centile, and reached the 10th centile in boys, but not in girls, at the age of 2 years. The 90th centile in boys with 22q11 deletion was similar to WHO standards; in girls, the 90th centile was closer to the 50th centile of WHO standards (Figs. 3 and 4).

Final adult height and weight measurements were obtained from 19 females and 6 males with ages 18– 45 years. Average height ($\pm$1 SD) was 152 ± 5.8 cm in females, corresponding to the 10th centile of WHO standards. Measurements ranged from 143 to 162 cm. For males, average adult height was 166 ± 4.1 cm (20th centile for

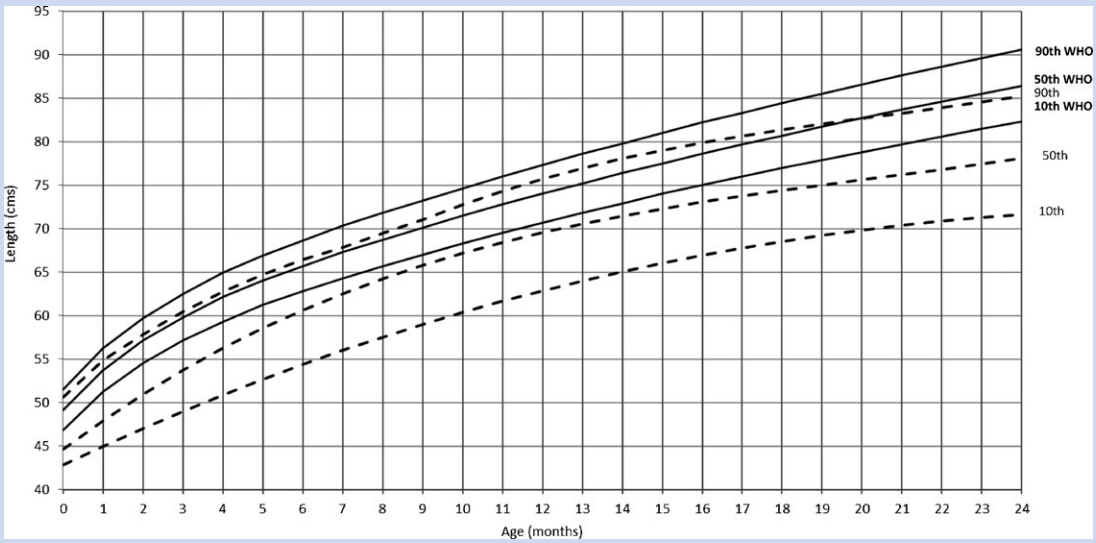

FIG. 3. Length in girls from 0 to 24 months. Solid lines represent the 10th, 50th, and 90th centiles of WHO Growth Standards. Dotted lines represent the same centiles in girls with 22q11 microdeletion.

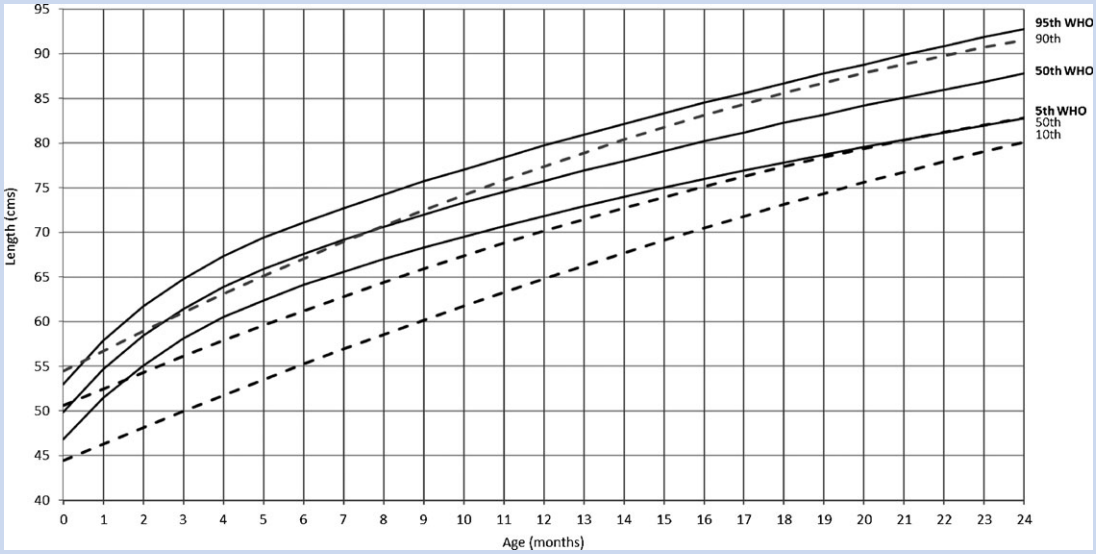

FIG. 4. Length in boys from 0 to 24 months. Solid lines represent the 10th, 50th, and 90th centiles of WHO Growth Standards. Dotted lines represent the same centiles in boys with 22q11 microdeletion.

WHO standards) and ranged from 160 to 172 cm. These measurements are within the normal range for Chilean adults according to the 2009–2010 National Health Survey that collected data from a representative sample of over 5,000 individuals throughout the country [Ministerio de Salud de Chile, 2011]. Average weight in adult females was 57 kg, resulting in an average BMI of 23.5 (median 24.1, range 16–33). Six females (31.5%) had BMI of 25 or greater; three of them were greater than 30. Weight average was 56.2 kg in males, with an average BMI of 20.3, median of 20.3, and range of 18.1–22.7. These values were lower than for adult Chilean population.

DISCUSSION

We report on growth data from a relatively large number of Chilean infants with 22q11 microdeletion syndrome, and showed that this group had slower growth in height and weight during the first 2 years of life, compared to WHO standards. The 50th centile in height for age in girls and boys with the deletion was similar to or lower than the 10th centile of gender specific WHO growth curves. These results are similar to those published by Digilio et al. [2001] and Shprintzen et al. [2008] in patients from Italy and the USA, respectively, with the majority of patients growing below the 10th centile for standardized norms in infancy.

We did observe a trend toward increase in boys' weight at 24 months of age, when the distribution tended to be closer to that of non-deleted children. A similar tendency has also been described in the two studies mentioned above, that show an increase in weight in childhood resulting in a higher frequency of overweight school-age children and adolescents with the deletion. We observed a high frequency of obesity in adult females in our series. This was not observed in males, probably because only six were included.

The study is limited by the number of patients and measurements available, as well as by the retrospective nature of the data. In addition, measurements were collected at several health care centers, which may affect consistency of the procedure, but all clinics follow standardized national guidelines for anthropometric assessment [Ministerio de Salud de Chile, 2007] and thus the results presented here are likely to reflect the reality of clinical pediatric practice in primary as well as tertiary centers.

The cumulative evidence shows a distinct growth pattern in patients with 22q11 microdeletion consisting of slow growth in infancy, evolving to a gradual an improvement in height velocity that results in final adult heights in the low normal range. A tendency to greater rise in weight is observed, resulting in an increased risk of obesity. It is unclear whether this growth pattern is an intrinsic manifestation of the syndrome, or it is secondary to other clinical features, such as feeding difficulties that are very common in infancy and later subside. Recognition of this pattern emphasizes the need for dissemination and use of specific growth curves, as is commonly used for other syndromes [Styles et al., 2002; Butler et al., 2011; del Pino et al., 2011] and should prompt clinicians and families to develop preventive strategies designed to support growth in infancy and prevent the development of obesity in adolescents and adults with this frequent syndrome.

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