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ORIGINAL ARTICLE

Longitudinal Study of Growth of Children With Unilateral Cleft Lip and Palate: 2 to 10 Years of Age

Ilza Lazarini Marques, M.D., Ph.D., John Nackashi, M.D., Ph.D., Hilton Coimbra Borgo, M.D., Ph.D., Angela Patrícia Menezes Cardoso Martinelli, M.D., M.S., Luiz de Souza, Ph.D., Jeniffer de Cássia Rillo Dutka, Ph.D., William N. Williams, Ph.D., Maria Inês Pegoraro-Krook, Ph.D.

Objective: **To study the growth of children with complete unilateral cleft lip and palate (UCLP) from 2 to 10 years of age and to assess whether growth varied from that of children without UCLP (typical children).**

Design: **Physical growth was one of the outcome measures of a National Institutes of Health–sponsored longitudinal, prospective clinical trial conducted by the University of Florida and the University of São Paulo.**

Setting: **Hospital of Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC-USP), Bauru, Brazil.**

Main Outcome Measures: **Height and weight were prospectively measured for 360 healthy children with UCLP who were nonsyndromic, belonged to median socioeconomic status, and received health care at HRAC-USP. To compare growth of children with UCLP to that of typical children, growth curves for UCLP were developed and compared with World Health Organization curves for 2006 and 2007, which were used as reference for typical children. Third-degree polynomials were used to explain the relationship of length and weight with age. Confidence limits of 95% were used for the mean curve using the statistic $Z \sim N(0,1)$.**

Results: **Children with UCLP from 2 to 10 years old presented height and weight growth curves similar to those of typical children for both genders.**

Conclusion: **Children with UCLP from 2 to 10 years old presented physical growth similar to that of typical children.**

KEY WORDS: *body height, body weight, cleft lip, cleft palate, growth, outcome assessment*

Normal physical growth of infants and children is one of the key indicators of good health (Vesel et al., 2010). Inadequate physical growth in young children with cleft lip and palate (CLP) may indicate a number of health-risk etiologies, including nutritional status concerns, chronic health conditions, genetic conditions or a component of a syndrome, growth hormone deficiency, or other endocrine conditions. CLP may also be associated with a deficiency in the development of the pituitary and with brain structural abnormalities (Tuohy and Franklin, 1984; Nopoulos et al., 2002; Van der Plas et al., 2010). The intent of this study was to verify the presence or absence of growth impairment in children with complete unilateral CLP (UCLP).

Reports indicate that growth problems are more frequent in children with CLP and isolated cleft palate than in children with isolated cleft lip and typical children (Felix Schoollaart et al., 1992; Lee et al., 1997; Montagnoli et al., 2005; Zarate et al., 2010). The growth problems in the first years of life have been attributed to environmental factors, including the high frequency of respiratory and middle ear infections (Seth and McWilliams, 1988) and the difficulty often encountered in feeding children with cleft palate (Drillen et al., 1966; Coy et al., 2000; Gopinath and Muda,

Dr. Marques is Medical Director and Pediatrician, Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, SP, Brazil. Dr. Nackashi is Medical Director, Pediatrician, and Professor, University of Florida, College of Medicine, Gainesville. Dr. Borgo is Pediatrician, Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, SP, Brazil. Dr. Martinelli is Pediatrician, Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, SP, Brazil. Dr. Souza is Statistician and Professor, University of São Paulo, College of Medicine, Ribeirão Preto, SP, Brazil. Dr. Dutka is Speech/Language Pathologist and Professor, Communication Disorders Department, School of Dentistry of Bauru and Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, SP, Brazil. Dr. Williams is Speech/Language Pathologist and Emeritus Professor, University of Florida, Gainesville. Dr. Pegoraro-Krook is Chair, Speech/Language Pathologist, and Professor, Communication Disorders Department, School of Dentistry of Bauru and Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Bauru, SP, Brazil.

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Address correspondence to: Dr. Ilza Lazarini Marques, HRAC-USP, SVAPEPE-PC. Rua Silvio Marchione 3–20, 17012-900, Bauru-SP, Brazil. E-mail marquesi@usp.br.

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2005; Montagnoli et al., 2005; Marques et al., 2009; Zarate et al., 2010).

After 2 years of age, biological factors have a greater influence than environmental factors in regulating growth in typical children (Coy et al., 2000). In the literature there is speculation that growth hormone deficiency in children with CLP negatively affects growth during the second or third year of life (Laron et al., 1969; Rudman et al., 1978; Tuohy and Franklin, 1984). These findings, however, are controversial, as some authors report finding no association between CLP and growth hormone deficiency (Koster et al., 1984).

Several variables may be affecting the ability of investigators to ascertain the relationship between physical growth and CLP, including small retrospective studies, inclusion of different types of clefts, presence of anomalies, health risk factors, genetic conditions and syndromes, and low socioeconomic status (SES) of children. A well-designed study of physical growth patterns requires a large longitudinal design that excludes children with risk factors that may affect growth. Only children with the same type of cleft in a defined age range should be included, resulting in a homogeneous population. A prospective study adds to the strength of the findings. The growth pattern varies according to the age range; therefore, different age ranges should be considered a potential confounder in growth studies.

European, US, and Brazilian studies on nonsyndromic cleft prevalence in general demonstrated that UCLP is the most frequent single type of cleft, accounting for 30% to 45% of cases. Isolated cleft lip and isolated cleft palate each account for 20% to 25%. and bilateral CLP is the least common (about 10%); submucous and other clefts account for the rest (Mossey and Little, 20002; Montagnoli et al., 2005, Cymrot et al., 2010).

The objective of this article is to analyze the physical growth (height and weight) of a large sample of non-syndromic children with the most frequent type of cleft, UCLP, from 2 to 10 years of age, by gender, in a longitudinal and prospective study, and to compare their growth to that of typical children.

Methods

In 1994, the University of Florida Craniofacial Center, in collaboration with the Hospital of Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC-USP), Bauru, Brazil, initiated a 10-year clinical trial sponsored by the National Institutes of Health. This was a longitudinal, prospective, randomized, blinded, controlled study in children with UCLP. Subjects were randomly assigned to undergo either the Spina or Millard lip repair, the von Langenbeck or Furlow palatal repair, and to receive palatal surgery at 9–12 months or 15–18 months of age. The primary outcome measure was to determine which of two lip surgeries, which of two palate surgeries, and which of two palate surgery timings were superior in terms of speech outcomes. All children in this study had their palate repaired before 18 months of age. Physical growth (height and weight) was one of the outcome measures of this trial.

Weight and height were prospectively measured for 360 children. 212 (58.9%) were boys and 148 (41.1%) were girls, with complete UCLP, from 2 to 10 years of age, and whose families were determined to be in the median socioeconomic level. These children were followed through the HRAC-USP outpatient clinic using standardized techniques and protocols to measure height and weight. Children were excluded from the study if they had anomalies (involving cardiac, central nervous system, musculoskeletal, gastrointestinal systems), chronic disease, and genetic conditions or syndromes or if they belonged to a low SES.

All children in this study received care in the same facility by any one of three pediatricians. Weight was obtained with children clothed only in underpants, on standard scales with weekly calibration, accurate to a 10-g precision. Height was measured with a vertical anthropometer with the child standing up straight and barefoot and with a margin of error of 0.5 cm. The children were examined and measured at each return visit for reevaluations (postoperative) according to the clinical trial protocol. Measurements were obtained at 12-month intervals but the ages at the measurements were different among the children.

Following the HRAC-USP guidelines (Graciano et al., 1996), children were classified into high, medium, and low SES levels. This study sample had no children from high SES, and children from low SES were excluded. The SES was reevaluated at the 12-month return visit intervals.

World Health Organization (WHO) growth curves from 2006 and 2007 (WHO; 2006, 2007) were used as growth reference for typical children.

This study was approved by the Institutional Review Board at the University of Florida and by the Ethical Committee at HRAC-USP.

Statistical Analysis

Random-effects modeling estimated the mean height and weight of children over time using the restricted maximum likelihood method (Jennrich and Schluchter, 1986). Third-degree polynomials were used to explain the relationship of height and weight with age, and estimates of the covariances matrix for both anthropometric variables were based on the function of the second degree. The curves were fitted and compared to the corresponding curves of the WHO (2006, 2007) with 95% confidence intervals by graphical representation.

After estimating the parameters of the mean curve and the corresponding confidence limits, ages 2, 4, 6, 8, and 10 years were chosen for convenience to determine points on the graph and mapping curves. The values corresponding

TABLE 1 Means and Confidence Limits of 95%* of Height of Children With UCLP (Present Study Sample) and Mean Height of Typical children (WHO, 2006) by Gender at Age 2, 4, 6, 8, and 10 Years

		Height (cm)				
Gender	*Age (Years)*	*2*	*4*	*6*	*8*	*10*
Boys	UCLP (mean)	86.9	103.2	116.3	127.3	137.5
	WHO (2006, 2007)	86.5	102.2	115.4	127.9	138.6
	UCLP (IL)	86.4	102.7	115.5	126.3	135.9
	UCLP (SL)	87.4	103.7	116.9	128.3	139.1
Girls	UCLP (mean)	86.1	102.4	115.5	126.5	136.8
	WHO (2006, 2007)	85.0	100.8	114.7	127.6	138.0
	UCLP (IL)	85.6	101.9	114.8	125.5	135.1
	UCLP (SL)	86.7	103.0	116.2	127.6	138.4

* IL= inferior limit, SL= superior limit, UCLP = unilateral cleft lip and palate, WHO = World Health Organization.

to these points are presented in Table 1. For each of these ages we calculated the mean and the confidence limits (mean ± 1.96 SD). In the analysis methodology the confidence limits vary according to the size of the sample; the larger the sample, the closer to the mean (Dawson et al., 1980). We considered the distribution $Z \sim N(0, 1)$ because the sample of the study is relatively large; therefore, this statistical method was a good choice for the analysis. The points were allocated on the graph and connected by line segments together with the WHO curve (2006, 2007), enabling the visualization of any significant difference between the two populations by age group or in each of the numerous points between 2 and 10 years. Therefore, although we used the age points described earlier to construct the curves, the inference is valid for any age between 2 and 10 years. If the WHO (2006, 2007) growth curve is completely enclosed between upper and lower limit of the UCLP growth curves then the conclusion is that the UCLP curve does not differ statistically from the WHO (2006, 2007) growth curve.

Results

The difference between the mean height and its confidence limits for children with UCLP and the height of typical children (WHO; 2006, 2007) from 2 to 10 years of age can be seen in Table 1 and Figure 1a and 1b. In relation to Table 1, it is shown that the height of typical children (WHO; 2006, 2007) was not above the superior limit of children with UCLP but was below the inferior limit for some ages for both boys and girls (results in favor of children with UCLP). According to Figure 1a and 1b, the children with UCLP did not have significant impairment in height growth as the curves for typical children do not surpass the superior confidence limit of UCLP mean height growth curves for boys or girls.

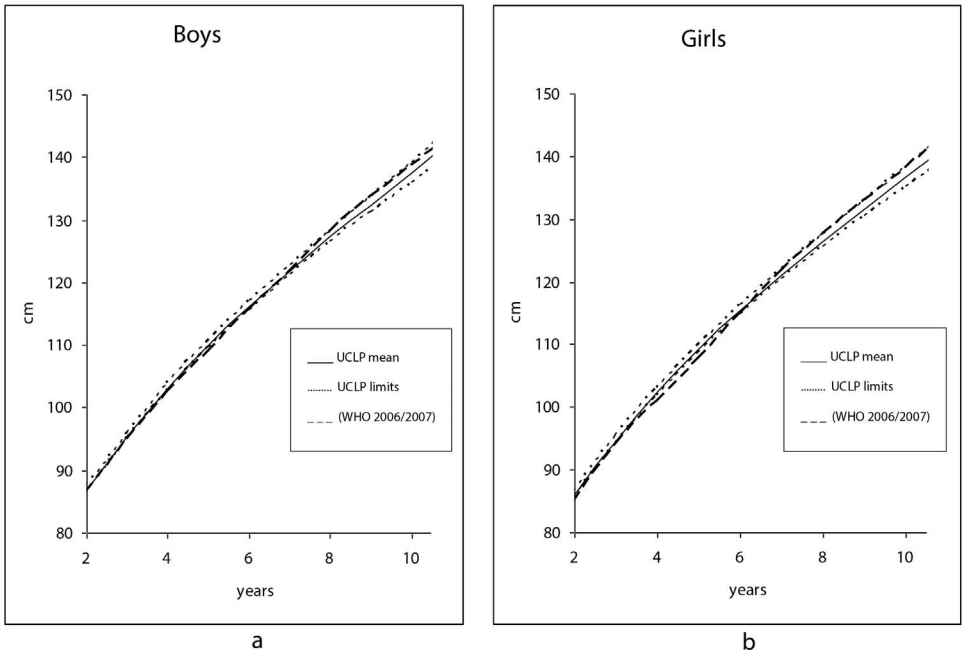

FIGURE 1 Mean height growth curves and 95% confidence limits of children with UCLP and mean height growth curves of normal population (WHO; 2006, 2007).

TABLE 2 Means and Confidence Limits of 95%* of Weight of Children With UCLP (Present Study Sample) and Mean Weight of Typical children (WHO, 2006) by Gender at Age 2, 4, 6, 8, and 10 Years

		Weight (kg)				
Gender	*Age (Years)*	*2*	*4*	*6*	*8*	*10*
Boys	UCLP (mean)	12.8	17.0	21.5	26.6	32.6
	WHO (2006, 2007)	12.7	16.2	20.7	25.6	31.9
	UCLP (IL)	12.6	16.8	21.1	25.9	31.4
	UCLP (SL)	13.0	17.3	21.9	27.2	33.8
Girls	UCLP (mean)	12.4	16.6	21.1	26.1	32.2
	WHO (2006, 2007)	12.1	15.8	20.4	25.6	32.9
	UCLP (IL)	11.7	15.9	20.2	25.1	30.6
	UCLP (SL)	13.0	17.3	21.9	27.2	33.8

* IL = inferior limit, SL = superior limit, UCLP = unilateral cleft lip and palate, WHO = World Health Organization.

Regarding weight, the differences between the mean and confidence limits of weight of children with UCLP and the weight of typical children (WHO; 2006, 2007) from 2 to 10 years of age are presented in Table 2. We also observed that the weight of typical children was not above the superior limit of children with UCLP for both boys and girls. Likewise, according to Figure 2a and 2b, the children with UCLP did not have significant impairment in weight growth as the growth curves of typical children (WHO; 2006, 2007) are first below the inferior limit (the difference was significant but in favor of children with UCLP) and later are limited by the superior and inferior UCLP weight growth curves for boys and are totally limited by superior and inferior limit for girls.

Discussion

The main contribution of this study is to present the first longitudinal growth data for weight and height for boys and girls between 2 and 10 years old on a large sample of children with the same type of cleft condition. The ideal approach would be to evaluate the children at the same ages and regular intervals to facilitate the statistical analysis but this was not possible. The HRAC- USP is one of the major reference centers for craniofacial malformations in Brazil, and it receives patients from distant locations. For this reason, return visits for postoperative reevaluations were established following the clinical trial protocol and availability of the family. A limitation of this study is that patterns of growth of length and weight cannot be determined for children with other types of cleft palate because this study only involved UCLP. Even with these limitations, this data set is one of the largest prospective and longitudinal growth studies ever published for 2- to 10-year-old children with CLP.

According to various studies in the literature, both UCLP and bilateral CLP are more common in the male gender. Isolated cleft lip is also more common among boys,

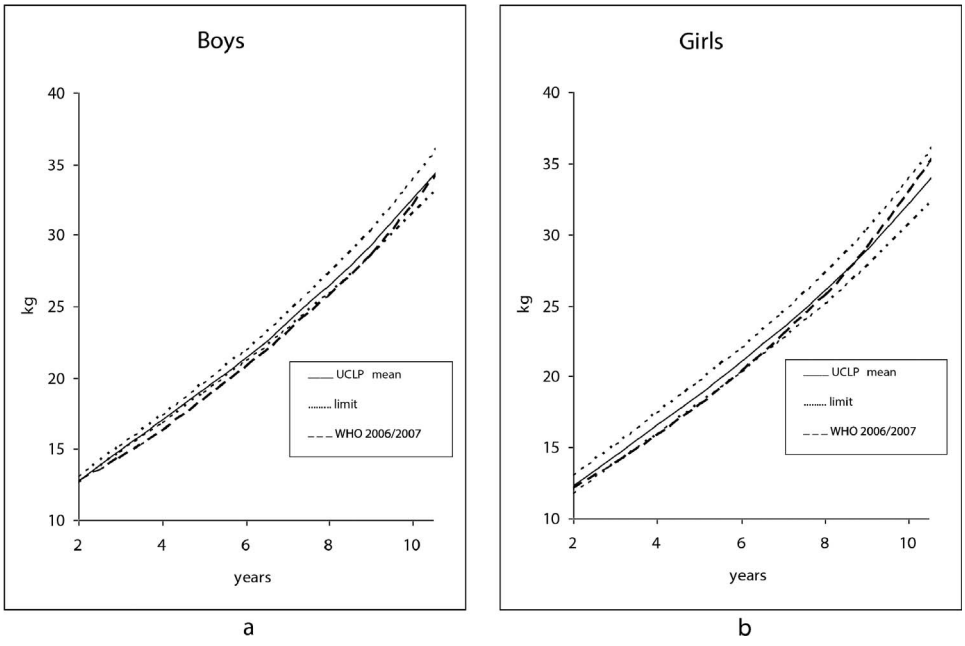

FIGURE 2 Mean weight growth curves and 95% confidence limits of children with UCLP and mean weight growth curves of normal population (WHO; 2006, 2007).

whereas isolated cleft palate is more common among girls. In this study we also observed a high prevalence of boys.

The present study shows that children with UCLP from 2 to 10 years old have body growth (height and weight) similar to that of typical children. In the first analysis of growth from birth to 2 years of age in these same children in Marques et al. (2009), this study group initially showed impairment in length and weight but presented catch-up growth by the end of the first year of life. Most studies on growth of children with CLP and for children with isolated cleft palate report physical growth deficiencies in length and weight, especially during the first year of life when the primary palatoplasty had not yet been done (Day, 1985; Jones, 1988; Seth and McWilliams, 1988; Lee et al., 1997; Pandya and Boorman, 2001; Gopinath and Muda, 2005; Montagnoli et al., 2005).

Few studies in the literature report growth in children with CLP who are older than 2 years, and most of them are retrospective or involve different types of clefts or a grouping of infants with older children and adolescents (Ranalli and Mazaheri, 1975; Cunningham and Jerome, 1997; Koltz et al., 2012). The most controlled study in the literature was performed by Nackashi et al. (1998); these authors assessed 112 Russian children with UCLP from 4 to 10 years of age in a prospective study and found no increased risk for short stature.

It is well recognized that CLP is a common component of numerous malformation syndromes (Cohen, 1978). Children with syndromes commonly have an increased incidence of short stature (Gorlin et al., 2001). Disregard for heterogeneity of the population sample with CLP could result in distortion of an association between physical growth and particular cleft types. Some types of cleft are more associated with syndromes, such as isolated cleft palate and median cleft lip (Cohen, 1978). The minimum variables that should be used to properly analyze growth patterns of children with CLP are sample size adequate for statistical analysis; same type of cleft; absence of associated anomalies, genetic conditions, syndromes, or chronic health conditions; defined age range; and SES that does not put the child at a poor health risk (this may vary by country).

The population of the present study was very homogeneous in that it focused on a group of healthy children in a defined age range, who belonged to median SES, and who had the predominant type of cleft. The reference population used (WHO; 2006, 2007), was the result of a multicenter study with typical children from different countries: Brazil, Ghana, India, Norway, Oman, and the United States. In the WHO (2006, 2007) study, children from low socioeconomic class or those with diseases that could interfere with growth were excluded (Onis et al., 2004). The WHO (2006, 2007) growth charts are recommended by WHO for growth evaluation of children from different countries and are also recommended as a reference for scientific studies on infant growth.

Some investigators have emphasized the importance of a precise diagnosis of the type of CLP for growth assessment using populations as homogenous as possible. They assumed that children with CLP without associated genetic syndromes have a growth curve in the normal range (Ross and Johnston, 1972). In contrast, other studies (Rudman et al., 1978; Ranke, 1989; Cunningham and Jerome, 1997; Lipman et al., 1999) have stated that children with congenital malformations or genetic syndromes assume their own growth pattern, which might differ from that of typical children, and represent groups with their own disease-specific growth pattern. Some of the investigators who studied growth of children with isolated CLP did not study a homogenous sample

The growth curves established in this study have demonstrated that the growth curves of children with UCLP are similar to the growth curves of typical children. They do not have a disease-specific growth pattern, and therefore the WHO 2006/2007 growth curves can be used as the reference for normal growth for children with UCLP in individual clinical evaluations.

Conclusion

We conclude that children with UCLP from 2 to10 years old do not present impairment in physical growth.

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