Standard Growth Curves in Prader-Willi Syndrome in Japan

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Abstract. We report standard growth curves in Japanese Prader-Willi syndrome (PWS) for height. Growth patterns for height are quite different between PWS and normal controls, showing the mean height in PWS ranging at −2SD of normal control data until pubertal age and dropping off far below −2SD of normal control after puberty. These data indicate that the pathogenesis of the short stature of PWS originates from both chromosomal abnormalities and hypogonadism. In addition to these factors we suspect that bone dysplasia seen in patients with this syndrome is also one of the factors in the short stature of PWS.

Key words: Prader-Willi syndrome, growth curves, short stature, bone dysplasia, hypogonadism

Introduction

The Prader-Willi syndrome (PWS) consisting of craniofacial anomalies, infantile hypotonia, hypopigmented skin, hypogonadism, abnormal eating habits, mental retardation, obesity, short stature, and small hands and feet was originally reported in 1956 by Prader, Labhart and Willi [1]. The exact cause of this syndrome is still obscure, but previous cytogenetic studies have shown that a half or more of patients have microdeletion at the 15q11-q12 region [2]. The parental origin of the del (15) in this syndrome is preferentially paternal in origin [3, 4], strongly suggesting a role for genetic imprinting in expression of PWS phenotype. In addition, karyotypically normal PWS patients sometimes demonstrate both of their normal homologous chromosomes 15 are of maternal origin [5]. The frequency of maternal hetero-disomy is suspected to be around 20% of all PWS [6], indicating that more than 70% of PWS originates from chromosomal abnormalities.

There have been a few anthropometric studies in PWS [7-10] and there has not been

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reported any significant difference in anthropometric data between individuals with and without 15q deletion [2, 10, 11]. Recently, Butler et al. reported the standards for selected anthropometric measurements including linear growth and weight in Caucasian PWS [12].

In this paper, we report standardized curves for Japanese PWS patients for length and height.

Subjects and Methods

We studied 84 Japanese patients (ages 1-16 years, 54 males and 30 females) who were clinically diagnosed as PWS, showing infantile hypotonia and feeding difficulty, hypogenitalism, hypopigmented skin, psychomotor retardation, early childhood obesity, and small hands and feet. Approximately one third of the patients were on a calorie-restricted diet at the time of the examination. Longitudinal data of length or height were collected on all individuals for a mean period of 7.3 years for males and 6.1 years for females.

High resolution chromosome analysis was performed on 76 patients. Forty-eight subjects had chromosomal abnormalities, including 45 subjects with del (15) (q11.1q12), 2 with 45t (15;15)(p11.1;q11), and 1 with del (15)(q11.1q12)+ inv dup(15)(q11.2;q11.2). Twenty-eight subjects had normal karyotypes, but 2 subjects showed maternal heterodisomy.

The length and height data collected in a longitudinal mode were arranged to obtain height at each month of age in each case by following the mathematic method, instead of the graphic method, using a growth curve drawn by an eye-fitting technique. This method is the same as Suwa used when he described the standard curves of Japanese Turner’s syndrome [13].

When $Y_A$ and $Y_B$ are the height at the time (age in months) of $X_A$ and $X_B$ respectively, the height at $X_t$ between $X_A$ and $X_B$ is interpolated by the following formula, so long as the interval of the two points of age is within 48 months. $Y_t = \frac{\log(X_t+1) \times (Y_A - Y_B) + \log(X_B+1) \times Y_A - \log(X_A+1) \times Y_B}{\log(X_B+1) - \log(X_A+1)}$. $Y_t$ at each month of age between $X_A$ and $X_B$ was calculated. In order to smooth these data, $Y_t$ was corrected by the method of “moving mean” averaging the calculated height at 13 points between six months before and after the age of $X_t(Y_{t-6}, Y_{t-5}, \ldots Y_{t-1}, Y_{t+1}, \ldots Y_{t+5}, Y_{t+6})$.

Their longitudinal data of length and height were plotted on our cross-sectional growth curves of Japanese children [14].

Results

The mean height at each month of age from birth through 16 years was calculated in the groups with normal and aberrant karyotype (data are not shown here). There was no significant difference between the two groups.

Figures 1 through 4 show standardized curves of anthropometric variables for male and female patients with PWS and for healthy individuals. Figures 1 and 2 are the curves from 0 through 48 months (four years) of age and figure 3 and 4 are from 0 through 192 months (16 years) of age, respectively. For the male until four years old, the mean length and height closely approximates the normal $-2SD$ (Fig. 1), and by 13 years of age, the mean height falls below the normal $-2SD$ and continues to drop off relative to the normal curve (Fig. 3). Similarly, in female patients with PWS, the mean length or height ranges the $-2SD$ of normal control (Fig. 2), and by 10 years old, the mean height falls below the normal $-2SD$ and continues to drop (Fig. 4).

Discussion

Standardized curves were produced for length and height for both male and female patients with PWS. Several authors have reported that there is no significant difference
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Fig 1. Longitudinal growth data from 0 to 48 months of age for 54 male patients with PWS plotted against Japanese male standard. Shaded area implies mean ±2SD of healthy normal control.

Fig 2. Longitudinal growth data from 0 to 48 months of age for 30 female patients with PWS plotted against Japanese male standard. Shaded area implies mean ±2SD of healthy normal control.

Fig 3. Longitudinal growth data from 0 to 16 years of age for 54 male patients with PWS plotted against Japanese male standard. Shaded area implies mean ±2SD of healthy normal control.

Fig 4. Longitudinal growth data from 0 to 16 years of age for 30 female patients with PWS plotted against Japanese male standard. Shaded area implies mean ±2SD of healthy normal control.

in anthropometric data between individuals with and without chromosomal aberrations [2, 10, 11]. We came to the same conclusion. The mean length or height of the individuals with PWS approximates around the normal −2SD until prepubertal age, indicating that the pathogenesis of the short stature of PWS comes from genetic factor(s). The fall-off in linear growth occurs after 13 years of age in male and after 10 years of age in female
patients, probably reflecting the lack of pubertal growth spurt in patients with PWS.

In addition to the above factors as the pathogenesis of the shortness in PWS, we speculate one more factor, a bone dysplasia. We often observe mild bone dysplasia in individuals with PWS and there are also a few reports describing bone abnormalities [15]. Similarly, mild bone dysplasia is known in Turner’s syndrome and is suspected to be one of the causal factors of short stature in Turner’s syndrome.

Anthropometric standards have been developed for several syndromes and have been used successfully in the medical management of patients. There is recent evidence for growth hormone deficiency at least in some patients with PWS and favorable responses to growth hormone therapy [16]. The use of our anthropometric standards may be helpful in those patients who have PWS being treated with growth hormone. We show one female patient with PWS treated with growth hormone and plotted her growth record on the standard growth curves of the normal female (Fig. 5). It is difficult to identify whether this treatment is successful or not, however, when we plot her data on PWS specific growth curves (Fig. 6) the therapeutic usefulness is apparent.

Finally in this work we tried to make standard growth curves with PWS, but the number of the older children with this syndrome was not enough to draw perfect growth curves. We would like to improve these growth curves by collecting more data on older patients with PWS in the future.

References

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