

ORIGINAL ARTICLE

WILEY

Physical assessment and reference growth curves for children with 46, XY disorders of sex development

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Funding information

National Key Research and Development Program of China, Grant/Award Number: 2016YFC0901505; Research of Biological Medicine and Life Science Innovation, Capital Residents Health Project- Etiological Diagnosis of 46, XY DSD, Grant/Award Number: Z15110200390000

Received: 13 July 2017

Accepted: 25 September 2017

Abstract

Importance: Impaired growth is an important factor in patients with disorders of sex development (DSD).

Objective: To profile the growth of children with 46, XY DSD.

Methods: We compared heights between 46, XY DSD children and normal boys and obtained growth curves for DSD using the λ -median coefficient of variation method. The study subjects were categorized into groups with good response and poor response to the human chorionic gonadotrophin (HCG) test according to testosterone levels and were compared height standard deviation scores (HtSDS) with normal boys.

Results: A total of 571 children with noncongenital adrenal hyperplasia (CAH) 46, XY DSD were enrolled in this study. The overall HtSDS for the DSD subjects were -0.031 ± 1.202 . The HtSDS of DSD boys were lower than those for normal boys among multiple age groups since early infancy. In children aged ≥ 12 years, the HtSDS values were significantly lower than the normal reference values for boys of the same age in both the good and poor response groups ($P = .025$ and $P = .003$, respectively). The HtSDS in the poor response group was generally lower than the normal reference value ($P = .017$). The average HtSDS values in the poor response groups were lower than those in the good response groups across multiple age groups.

Interpretation: Growth retardation was evident in boys with non-CAH 46,XY DSD in early childhood and puberty. The level of growth retardation was related to testosterone level. DSD-specific growth curves can improve our understanding of growth dynamics and minimize the scope for bias in the assessment of growth in these children.

KEYWORDS

curve, disorders of sex development, growth, testosterone

1 | INTRODUCTION

The term disorders of sex development (DSD) is defined as congenital conditions in which development of chromosomal, gonadal, or

anatomic sex is atypical.¹ DSD is a heterogeneous condition in terms of both its etiology and its clinical manifestations, and a gene molecular diagnosis is possible in only a small proportion of affected children. Among DSDs, 46, XY DSD accounts for most cases of unknown etiology.¹ Height increase in children with 46, XY DSD is

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affected by abnormal testosterone levels, and gonadal dysplasia is associated with DSD impacts on the individual's physical development from the prenatal period through to adulthood.^{2,3}

In addition to abnormal sexual development, impaired growth is additional key concerns in patients with DSD. We previously found that children with DSD were on average shorter than the normal reference standard for their age.⁴ Whether or not children with DSD should undergo surgical removal of dysplastic gonads during childhood is a contentious issue. Some studies have shown that early removal of gonads appeared to protect against gonadal malignancy, while other studies emphasized the importance of early gonadal function for bone growth in these children.⁵⁻⁹ Han et al assessed the heights of patients with complete androgen insensitivity syndrome and found that individuals who underwent gonad removal after adolescence or during adulthood were taller than those whose gonads were removed in the prepubertal phase,¹⁰ suggesting that the sex hormones had a positive effect on height gain during the prepubertal period.

Sex hormone deficiencies in prepubertal DSD children appear to be inextricably linked to growth. 46, XY DSD includes a variety of diseases, such as 5- α reductase deficiency, androgen insensitivity syndrome, congenital adrenal hyperplasia (CAH), and gonad dysplasia. These sex hormone abnormalities affect the growth of DSD children, and evaluating the growth patterns of DSD children against reference standards developed for normal children may thus not be valid. Excess testosterone will promote the growth of DSD children in childhood, but because their epiphyseal plates close earlier than those of healthy children, their final heights will be short. In comparison, testosterone deficiency is a direct cause of short stature. The severity of the defect and testosterone levels may thus vary, even within diseases with the same etiology, and the classification of growth curves for each disease is not necessarily helpful; the growth curve depends on the testosterone levels, rather than the specific disease. We therefore excluded patients with CAH because of high testosterone level from the current study.

To the best of our knowledge, no previous studies have quantified the growth patterns of children with DSD. This study therefore aimed to profile the physical developmental patterns of 0-16-year-old Chinese children with 46, XY DSD and to provide a reliable reference against which to assess the growth of these patients.

2 | SUBJECTS AND METHODS

2.1 | Study population

Data were obtained from the hospital registration database for 571 patients with 46, XY DSD who visited the Endocrinology Department of Beijing Children's Hospital between 2009 and 2015.

2.2 | Inclusion criteria

Children aged 0-16 years who were diagnosed with non-CAH 46, XY DSD, gonads were testes, presented micropenis and/or

hypospadias and/or cryptorchidism, reared as a boy or girl, and who had not received hormone replacement therapy were eligible for inclusion. Among the 46, XY DSD subjects, some of them had precise etiologic diagnoses, including 5 α -reductase type-2 deficiency in 19 cases and androgen insensitivity syndrome in 28 cases, but most were undiagnosed.

2.3 | Exclusion criteria

Patients with 46, XX DSD, sex chromosome DSD, 46, XY DSD with ovaries or ovotestes and those diagnosed with CAH were excluded from the study. Patients who were small for gestational ages, and those with pituitary hormone deficiency, hypothyroidism, malformations, disproportionate statures, and skeletal abnormalities disease were also excluded.

2.4 | Diagnostic criteria and DSD classification

Cases were diagnosed according to the diagnostic criteria and classification of DSD of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology.¹

2.5 | Outcome measures

We assessed the age-stratified physical development parameters of the patients. Clinical data, including physical parameters, age and birth history, obstetric history of the patient's mother, DSD history of the past three generations, and parental height, were recorded. All measurements were performed using standard anthropometric equipment and methodologies. Adherence to standardized procedures and quality control were ensured under the supervision of an endocrinologist. Height was measured as supine length in children aged <3 years and as orthostatic height in those ≥ 3 years of age. Each patient's height and weight were measured three times by an endocrine nurse, and the average value was taken.

Reference height- and weight-standardized growth charts for Chinese children and adolescents aged 0-18 years published in 2005 were used to calculate height standard deviation scores (HtSDS) and weight standard deviation scores (WtSDS).¹¹ $HtSDS = (\text{actual height} - \text{standard average height of boys in the same age group}) / \text{standard deviation of height of boys in the same age group}$. $WtSDS = (\text{actual weight} - \text{standard average weight of boys in the same age group}) / \text{standard deviation of weight of boys in the same age group}$. Body mass index (BMI) = body weight (kg)/height² (m²). Parental height was taken into consideration when assessing the height of their children. And child height was adjusted according to mid-parental height (hereditary median target height).

Chromosome examination was conducted by peripheral blood lymphocyte culture G-banding analysis at the 400-band level and checking for external genital malformations. Thirty cells from each patient were examined. Gonadal examination was conducted by pelvic ultrasonography (Philips Ultrasound iU22, Bothell, WA, USA).

2.6 | Growth curves

We described the growth index in each age category using the internationally accepted λ -median coefficient of variation method for generating standard curves to calculate the median, coefficient of variation, and coefficient of skewness after converting the data into a normal distribution using Box-Cox transformation.¹² These parameters of smooth curves and the required percentile were calculated using age as an independent variable. Growth curves (P3, P10, P25, P50, P75, P90, P97 percentile curves and $-3SD$, $-2SD$, $-1SD$, $0SD$, $+1SD$, $+2SD$, $+3SD$ standard deviation curves) for children in the 0-3-year and 3-16-year age groups were compared with the corresponding normal reference curves.

2.7 | Human chorionic gonadotrophin (HCG) test

Human chorionic gonadotrophin was administered at a dose of 1500 IU/d for 4 days by intramuscular injection.¹³ Blood samples (2 mL) were collected on the morning of the fifth day and tested for serum testosterone levels by enzyme enhanced chemiluminescence assay (SIEMENS IMMULITE 2000, Munich, Germany). A serum testosterone level

≥ 100 ng/dL was graded as a good response, while < 100 ng/dL was graded as a poor response. Based on these results, the study subjects were categorized into "good response" and "poor response" groups, respectively. HtSDS for children in these groups were compared with normal reference scores. All HCG tests were performed at the first visit.

2.8 | Ethics statement

Written informed consent was obtained from the parents/guardians and children (≥ 8 years old) in all cases. The study was approved by the ethics committee at Beijing Children's Hospital.

2.9 | Data analysis

The growth curves were calculated using LMS-chartmaker Light,¹⁴ and curves were drawn using GraphPad Prism 6 software. SPSS 17.0 software was used for statistical analyses. Data pertaining to quantitative variables were expressed as mean \pm standard deviation (SD). Intergroup differences were assessed using *t* tests. *P* < .05 was considered statistically significant.

TABLE 1 Physical parameters of children with 46, XY DSD (N = 511)

Age	N ^a	Height (cm)	Weight (kg)	BMI (kg/m ²)	HtSDS	WtSDS
0 mo	6	57.8 \pm 1.26	5.2 \pm 1.91	15.3 \pm 3.59	0.656 \pm 1.650	0.679 \pm 2.131
3 mo	20	65.9 \pm 4.50	8.0 \pm 1.02	18.5 \pm 1.61	0.366 \pm 1.479	0.507 \pm 1.048
6 mo	35	69.9 \pm 2.94	9.3 \pm 1.38	18.9 \pm 2.16	0.071 \pm 1.142	0.554 \pm 1.370
9 mo	45	73.8 \pm 3.25	10.2 \pm 1.18	18.7 \pm 1.89	0.004 \pm 1.246	0.665 \pm 1.121
12 mo	37	77.2 \pm 2.95	10.7 \pm 1.27	18.0 \pm 1.72	0.264 \pm 1.073	0.598 \pm 1.136
15 mo	32	80.5 \pm 3.80	11.2 \pm 1.34	17.4 \pm 1.86	0.241 \pm 1.288	0.450 \pm 1.134
18 mo	26	82.3 \pm 3.34	11.7 \pm 1.50	17.1 \pm 1.40	-0.118 \pm 1.077	0.292 \pm 1.201
21 mo	26	85.6 \pm 4.14	12.3 \pm 1.83	16.9 \pm 1.87	0.001 \pm 1.235	0.242 \pm 1.390
24 mo	37	88.9 \pm 5.48	13.3 \pm 1.89	16.8 \pm 1.39	0.106 \pm 1.566	0.568 \pm 1.367
30 mo	25	92.4 \pm 4.47	13.9 \pm 1.47	16.3 \pm 1.17	-0.227 \pm 1.192	0.169 \pm 0.971
3 y	36	98.5 \pm 4.73	16.4 \pm 2.28	16.9 \pm 1.64	0.111 \pm 1.164	0.825 \pm 1.291
4 y	32	105.1 \pm 4.10	18.1 \pm 2.68	16.3 \pm 2.13	-0.044 \pm 0.842	0.554 \pm 1.381
5 y	15	110.7 \pm 4.70	19.7 \pm 2.10	15.9 \pm 1.19	-0.583 \pm 1.013	0.015 \pm 0.787
6 y	13	120.9 \pm 3.33	24.0 \pm 2.99	16.3 \pm 1.66	0.341 \pm 0.653	0.655 \pm 0.960
7 y	19	126.3 \pm 5.95	28.3 \pm 6.01	17.6 \pm 2.72	0.200 \pm 1.101	0.830 \pm 1.372
8 y	14	133.1 \pm 8.00	34.4 \pm 10.06	19.1 \pm 4.50	0.206 \pm 1.382	1.007 \pm 1.702
9 y	19	136.0 \pm 6.76	37.1 \pm 10.18	19.9 \pm 4.50	-0.110 \pm 1.175	0.853 \pm 1.471
10 y	20	142.7 \pm 7.57	40.9 \pm 9.96	20.0 \pm 3.83	0.187 \pm 1.178	0.790 \pm 1.270
11 y	15	140.9 \pm 8.95	38.5 \pm 10.71	19.2 \pm 3.94	-0.821 \pm 1.202	-0.028 \pm 1.121
12 y	17	149.9 \pm 6.36	46.6 \pm 10.46	20.5 \pm 3.53	-0.405 \pm 0.906	0.332 \pm 1.081
13 y	11	154.4 \pm 7.43	49.1 \pm 9.03	20.6 \pm 3.29	-0.921 \pm 0.912	-0.042 \pm 0.795
14 y	7	157.8 \pm 4.82	50.5 \pm 5.51	20.3 \pm 2.54	-1.296 \pm 0.777	-0.328 \pm 0.498
15 y	4	164.0 \pm 6.44	59.4 \pm 14.09	22.0 \pm 4.56	-1.157 \pm 1.159	0.044 \pm 1.328
Total	511			17.95 \pm 2.77	-0.031 \pm 1.202	0.510 \pm 1.241

DSD, disorders of sex development; HtSDS, height standard deviation score; WtSDS, weight standard deviation score; BMI, body mass index.

^aData on height and/or weight were missing for some study cases, thus affecting BMI calculations.

3 | RESULTS

3.1 | Physical parameters

A total of 571 children with non-CAH 46, XY DSD were enrolled in the study. Their mean age was 4.21 ± 4.08 years (0.07-16.38 years), with 326 children (57.1%) <3 years of age. Genital phenotypes in these patients included small penis, hypospadias, testicular abnormalities, combined genitalia abnormalities such as small penis with hypospadias or cryptorchidism, or complete female vulva. Among the 571 cases, 60 were excluded because of nonavailability of height or weight data. The HtSDS, WtSDS, and BMI for the remaining 511 cases were -0.031 ± 1.202 , 0.510 ± 1.241 , and 17.95 ± 2.77 kg/m², respectively. The physical parameters of the study subjects in the different age groups are presented in Table 1. The average heights of the fathers and mothers of the children with 46, XY DSD were 172.1 ± 7.88 cm and 161.3 ± 5.01 cm, respectively, which were comparable with the normal reference standards for the Chinese population.

3.2 | Growth curves

Height percentile curves for the good and poor response groups and for normal boys are presented in Figure 1A. The height of the study subjects began to lag significantly behind that of normal

children from the age of 11 years, with the height lag being more pronounced in the poor response group. A scatter plot for height of subjects in the 0-16-year age group after quadratic curve fitting is shown in Figure 1B. The height of study subjects >7 years lagged behind that of normal boys, while the height curve in the poor response group was flat. The standard height curves for 0-3-year-old (N = 319) and 3-16-year-old (N = 236) study subjects are shown in Figures 2 and 3, respectively. The standard weight and BMI curves for 0-3-year-olds and 3-16-year-old subjects are shown in Figures S1-S4, respectively. Heights, weights, and BMI of three cases aged exactly 3 years were included in both groups.

3.3 | HCG standard test

The HCG standard test was conducted in 427 subjects, with a good response in 304 cases (height and weight values were missing in 24 and 6 cases, respectively), with associated HtSDS and WtSDS of 0.082 ± 1.212 (N = 280) and 0.594 ± 1.252 (N = 298), respectively. The response was graded as poor in 123 cases (height and weight values were missing in 3 and 4 cases, respectively), with associated HtSDS and WtSDS of -0.240 ± 1.090 (N = 120) (compared with the good response group, $P = .015$) and 0.309 ± 1.135 (N = 119) (compared with the good response group, $P = .035$), respectively.

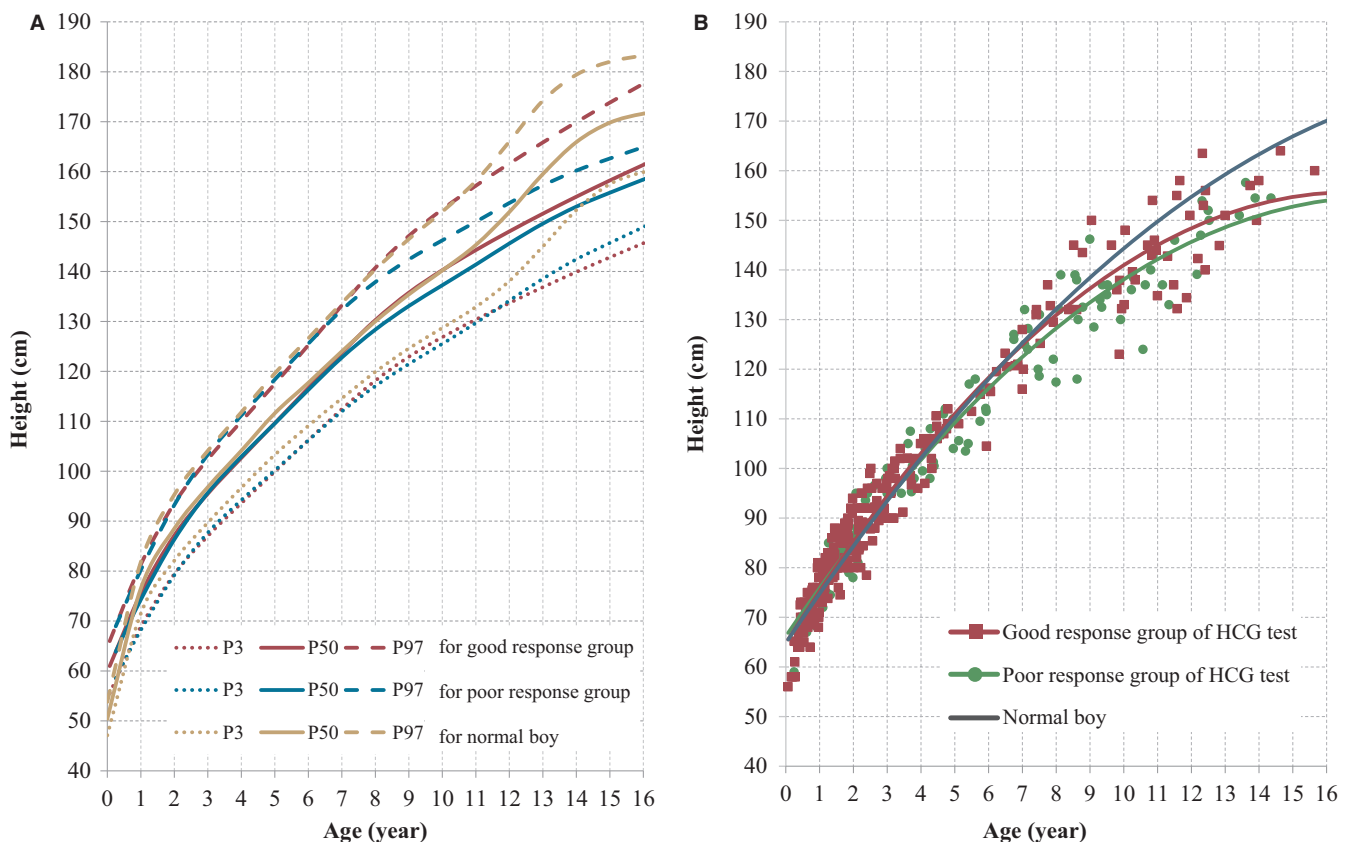


FIGURE 1 A, Height percentile curves for 46, XY DSD children and normal boys. B, Distribution and height trend in 0-16-y-old with 46, XY DSD. DSD, disorders of sex development

The two groups were stratified by age and assessed against the normal reference standards for boys (Table 2). The HtSDS in the poor response group was generally lower than the normal reference value ($P = .017$). In children aged ≥ 12 years, the HtSDS values were significantly lower than the normal reference values for boys of the same age in both the good and poor response groups ($P = .025$ and $P = .003$, respectively). The HtSDS values in both groups were lower than the average height for normal boys (HtSDS = 0) across multiple age groups since 6 months. The average HtSDS values in the poor response groups were lower than those in the good response groups, except for children aged 24, 30 months.

4 | DISCUSSION

In this study, we profiled the growth patterns of non-CAH children with 46, XY DSD and developed a specific standard growth curve to monitor the physical development of these children. A percentile growth curve represents a useful, convenient, and easy to interpret tool, while more rigorous evaluations can be carried out using a standard deviation growth curve, which allows for better discrimination.^{11,15,16}

Our results showed that the HtSDS of DSD was lower than the average height of normal boys in multiple age groups since early infancy, irrespective of the HCG response, although the average

HtSDS in the poor response group was lower than that in the good response group in most age groups. The HCG stimulation test only relatively reflects testicular Leydig cell function.

Most DSDs involve bone-age delay, and we previously found that height retardation was consistent with bone age.^{4,17} Tosson et al studied 45,X/46,XY DSD children and demonstrated growth retardation during the infant and adolescent periods, which eventually led to short stature.¹⁸ Bertelloni et al⁵ pointed out that the hormonal abnormalities in DSD patients may lead to abnormal bone growth, irrespective of racial differences. In a preliminary study in children with hypospadias, height and bone age increased after treatment, despite the shorter baseline heights of DSD children.¹⁹ In the present study, we observed a lag in height gain during infancy, with an insufficient growth spurt during adolescence, further substantiating the need for specific growth assessment of DSD children. These results suggest that even trace amounts of testosterone produced by normal boys in early childhood may play a key role in growth and development. Overall, the accumulated evidence suggests that children with DSD may benefit from hormone replacement therapy not only during puberty, but also during infancy. Optimal preoperative testosterone replacement therapy in 46, XY DSD infants is not only beneficial to the success of operation, but also for the subsequent physical development of these children.²⁰ We also speculated that testosterone treatment during infancy may benefit bone development by increasing bone density. Nevertheless, trace hormones in

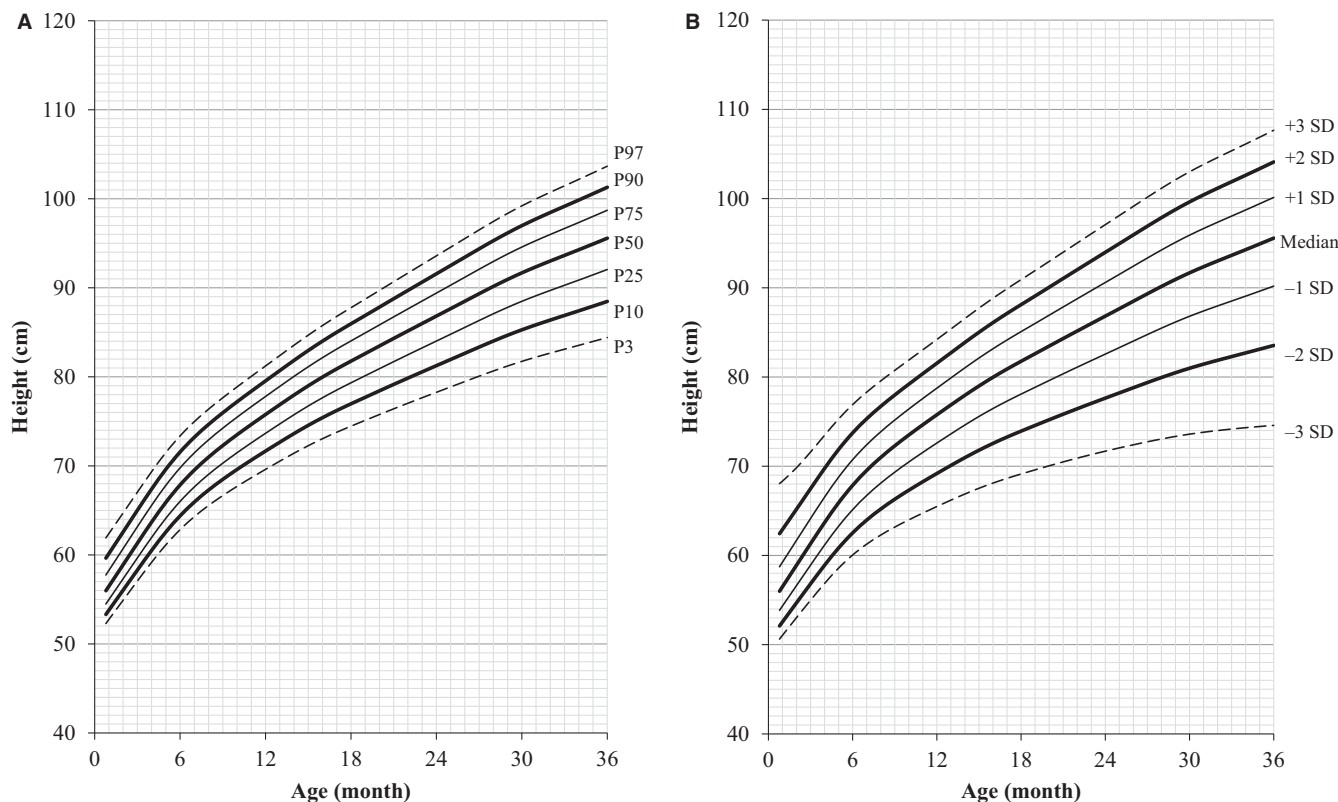


FIGURE 2 Standard height curves for 46, XY DSD children in the 0-3-y age group. A, Percentile curve; B, standard deviation curve. DSD, disorders of sex development

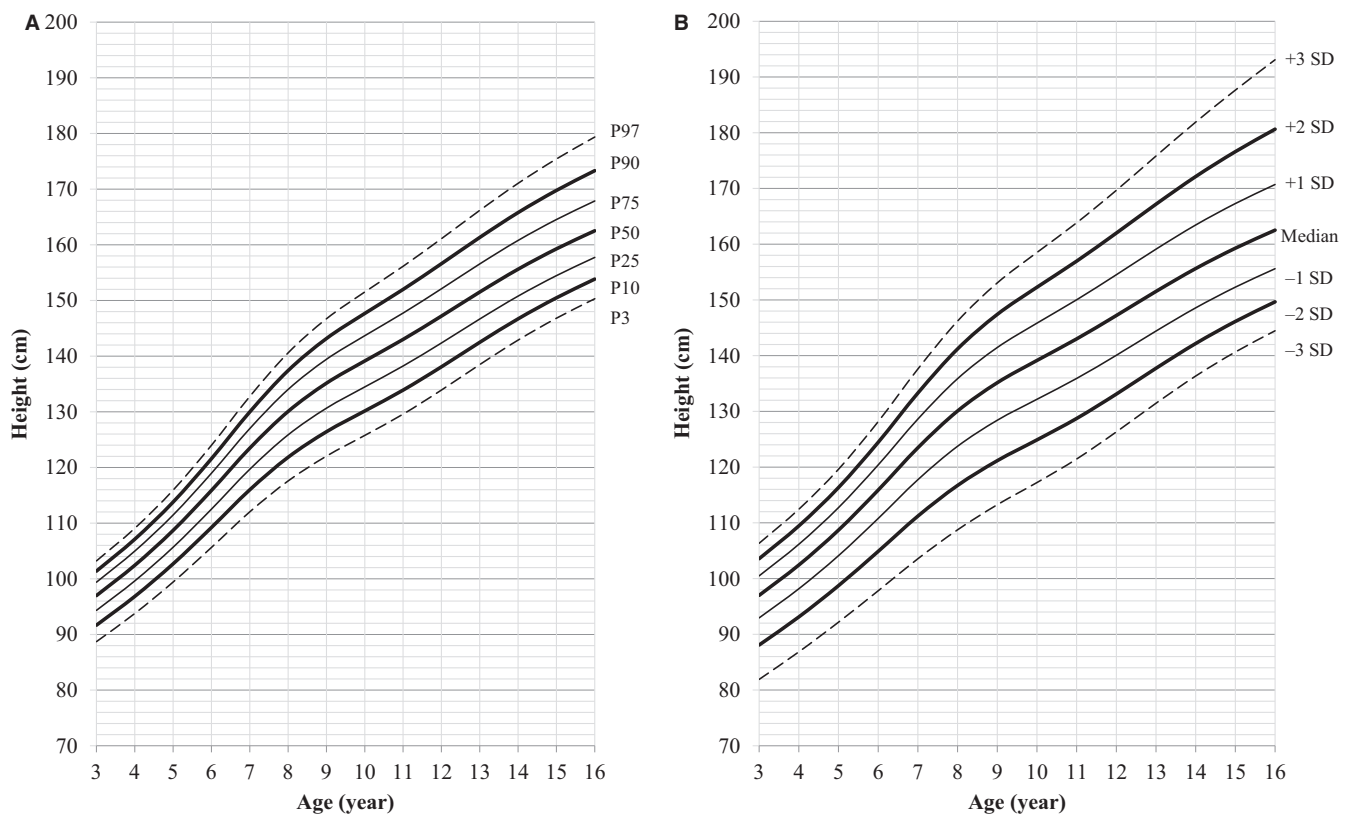


FIGURE 3 Standard height curves for 46, XY DSD children in the 3-16-y age group. A, Percentile curve; B, standard deviation curve. DSD, disorders of sex development

TABLE 2 Comparison of HtSDS between 46, XY DSD children and normal boys in the good and poor response groups for HCG standard test

Age	N	Good response group vs normal boys		N	Poor response group vs normal boys	
		mean \pm SD	P		mean \pm SD	P
0 mo	16	0.656 \pm 1.465	.094	2	0.546 \pm 0.583	.412
6 mo	59	-0.005 \pm 1.184	.974	6	-0.491 \pm 1.509	.461
12 mo	41	0.390 \pm 1.087	.027*	12	-0.152 \pm 1.024	.617
18 mo	33	0.099 \pm 1.210	.643	12	-0.567 \pm 0.994	.074
24 mo	22	-0.013 \pm 1.620	.970	6	0.386 \pm 1.617	.584
30 mo	17	-0.215 \pm 1.062	.673	3	0.631 \pm 0.777	.295
3 y	37	-0.020 \pm 1.025	.905	33	-0.119 \pm 0.939	.472
6 y	20	0.475 \pm 0.994	.046*	19	0.046 \pm 1.240	.873
9 y	23	-0.096 \pm 1.302	.727	17	-0.595 \pm 0.991	.025*
12 y	12	-0.758 \pm 1.033	.025*	10	-0.937 \pm 0.730	.003*
Total	280	0.082 \pm 1.212	.259	120	-0.240 \pm 1.090	.017*

HtSDS, height standard deviation score; DSD, disorders of sex development; HCG, human chorionic gonadotrophin; SD, standard deviation.

* $P < .05$.

infants and young children may have a positive effect on height. The growth curves determined in the current study indicate that shorter stature in DSD compared with normal children is associated with sex hormones. Testosterone supplementation in infants and young children may thus have a positive effect on height. The curve produced

in the current study thus represents the natural reference standard for this group.

This study had some limitations. Although this study represents the first large-scale study of Chinese children with 46, XY DSD, all the cases were sourced from a single institution. However, patients

were referred to this center from other institutions across the country, thus reducing the impact of this issue. Secondly, the data of this study were obtained from clinical practice, and the heterogeneous age distribution was inevitable but a limitation. Thirdly, if we can accumulate enough samples to data every given single disease, it would be more precise for the growth assessment.

In summary, we charted the physical growth curves of children with non-CAH 46, XY DSD to provide objective data and standards against which to evaluate their growth and development to help guide assessment precisely. Furthermore, 46, XY DSD-specific growth curves will improve our understanding of the growth dynamics and minimize the scope of bias in the growth assessment of children with 46, XY DSD.

ACKNOWLEDGMENTS

We thank Dr. Boya Liu and Miao Qin for performing data entry and data cleaning in this study. This work was supported by the National Key Research and Development Program of China 2016YFC0901505 and Research of Biological Medicine and Life Science Innovation, Capital Residents Health Project- Etiological Diagnosis of 46, XY DSD (Z15110200390000).

CONFLICT OF INTEREST

None of the authors has any conflicts of interest to declare in relation to this study and manuscript.

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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: Wu D, Chen H, Gong C. Physical assessment and reference growth curves for children with 46, XY disorders of sex development. *Pediatr Invest*. 2017;1: 13-19 . <https://doi.org/10.1002/ped4.12010>