Height Standard Deviation Score is Related to Karyotypes and Birth Weight in Girls with Turner Syndrome

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Abstract

Objectives: The purpose of this study was to evaluate clinical characteristic of girls with Turner syndrome (TS) and to search for associations between phenotype and birth weight or karyotypes. *Subjects and methods:* Subjects included 60 TS girls underwent growth hormone (GH) stimulation testing for short stature. All patients performed provocative tests with a combination of at least two of the following: arginine, levo-dopa or insulin. Cytogenetic finding, height, weight, insulin-like growth factor (IGF)-1, IGF-binding protein (IGFBP)-3, peak GH after stimulation were collected. *Results:* The mean age at diagnosis was 10.9±3.5 years. Thirty-one cases had 45,X, which accounted for 51.7% of total group. The patients were divided into two groups by their karyotypes: 45,X group and miscellaneous karyotypes (MK) group. There were no differences in age at diagnosis, weight, body mass index (BMI), height of their parents, incidence of GH deficiency (GHD), birth weight, basal luteinizing hormone and follicle stimulating hormone levels, IGF-1 and IGFBP-3 levels between two groups. However, height standard deviation scores (SDS) at diagnosis were -4.13±1.44, -3.12±1.3 for 45,X and MK group respectively (P=0.014). The incidence of ovaries absence in 45,X group was higher than MK group (33.3% vs. 12.5%, P=0.046). There was no correlation between height SDS and GH peak values (r=-0.182, P=0.182), IGF-1 (r=-0.075, P=0.583)and IGFBP-3 (r=-0.019, P=0.891). Birth weight was positively related to their height SDS and weight SDS (r=0.364, P=0.007; r=0.378, P=0.005) respectively. There were no correlations between birth weight and BMI, IGF-1 and other indexes. *Conclusions:* Karyotypes and birth weight have important impact on height SDS in TS girls.

Key words   Birth weight; Growth hormone; Karyotype; Short stature; Turner syndrome

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Introduction

Turner syndrome (TS) defines females who have lost an entire sex chromosome or a portion of the X-chromosome. The prevalence of TS has been estimated as approximately 1 in 2500 live female births. Short stature and ovarian failure are characteristic features of TS.[1] The etiology of short stature in TS is still unclear. The growth impairment in the majority of TS individuals is not due to growth hormone (GH) deficiency although a small minority of TS girls may manifest classic GH deficiency (abnormal GH concentrations after pharmacologic provocation).[2,3] The GH-insulin-like growth factor (IGF) − IGF binding protein (IGFBP) axis is profoundly disturbed in TS, with a partly normalising effect of sex hormone replacement therapy

(HRT).[4] Haploinsufficiency for the short stature homeobox-containing gene (SHOX) was found to also contribute to the marked short stature in TS.[5] However, the degree of short stature observed with simple haploinsufficiency for the SHOX gene is not as severe as that in TS patients, which suggested that haploinsufficiency for additional genes located on the X-chromosome also contribute to the growth retardation in TS.[6] The nature of the GH-IGF-IGFBP axis in Chinese TS girls without HRT still needs to be further investigated.

Pharmacologic provocation tests for GH are not recommended unless the girl's growth is clearly abnormal relative to that expected for TS determined by plotting lengths and heights on TS-specific growth curves.[3] However, there is no normative growth charts for Chinese TS girls, it is difficult to decide whether provocation tests should be made or not. Second, in any cases, clinicians should emphasize health priorities than height in TS; height is not validated as a surrogate measure for TS treatment.[7] Spontaneous secretion of GH in the patients with TS was lower than that of the short normal prepubertal girls.[8] GH deficiency (GHD) is associated with increased premature mortality, especially from cardiovascular and cerebrovascular diseases. Our previous researches found GH treatment improved cardiac function.[9] At last, congenital or acquired cardiological problems occur commonly in TS. They are potentially progressive and justify aggressive preventive management from childhood onwards. Prospective studies are required to provide more information about the utility of treatments liable to prevent or delay aortic dilatation in TS. The heart is a major target organ for GH; higher numbers of IGF receptors are present in the heart. Therefore, we hypnoses GH deficiency may involve in the cardiovascular morbidity in TS girl. It could be one pathway to regulate GH concentration for preventing TS patients from cardiovascular and cerebrovascular diseases. Taken above factors into serious consideration, we assume it is still useful to improve GH provocative test in TS girls.

Birth parameters are one of the more important predictors of body height in adult life. Children with low birth weight (LBW) are an essential and heterogenic group of patients diagnosed because of short stature.[10] Subjects with LBW demonstrated an increase in mortality from coronary heart disease in adulthood, and this observation was followed by many studies on long term adverse effects of intrauterine growth retardation.[11] Body mass deficit at birth is one of the characteristic features in TS. It is still not well known if low birth weight has adverse effects on physical growth in children with TS.

Cohen et al reported that final height of adults with Turner's syndrome, never treated with GH, was related with karyotype patterns.[12] Ranke et al found that height and age at GH start, the responsiveness to GH and age at puberty determine near adult height in 987 TS children. However, Karyotype had no influence on near adult height outcome.[13] Ovarian function in TS patients is associated with the specific karyotype.[14] Little is known about the relationship between karyotype and height and other phenotypes in Chinese TS girls without treatment.

The purpose of this study was to evaluate the clinical, hormonal, cytogenetic characteristics and to search for the associations between phenotype and birth weight or karyotypes in 60 TS patients with short stature who performed growth hormone GH provocative tests.

Subjects and Methods

Definition

Short stature is defined as height more than 2 standard deviations below the mean for age and gender.[15,16] which corresponds to the shortest 2.3% of individuals. Duration of short stature means the period from the age of first presented with short stature to the age that were diagnosed as TS. GHD is confirmed by a GH response to insulin tolerance test, and dopamine/arginine stimulation test of less than 10 μg/liter.[17] Low birth weight (LBW) is a birth weight ≤2500 g for full-term gestation. Height or weight standard deviation (SD) scores were calculated as follows: SD score = (patient value − mean value for age- and sex-matched normal subjects) ÷ SD of the value for age- and sex-matched normal subjects.

Subjects

The study was designed by the authors and was approved by the human ethic committees of the Children's Hospital of Zhejiang University School of Medicine. Patients were recruited from our paediatric endocrine clinics between 1st January 2004 and 30th June 2011. Written informed consent was obtained from the patients' parents or guardians. Criteria for study entry included a karyotype diagnosis of TS with short stature for the first time. Additional criteria were no recent or concurrent treatment that might influence growth. Children with severe chronic illness were excluded. Children receiving medications that may affect endogenous GH secretion, including oral or inhaled corticosteroids, antipsychotic medications were also excluded. Subjects in the final analysis included 60 TS patients and underwent GH stimulation testing, without sex steroid pretreatment.

Data Collection

Data relating to features associated with TS were collected. Height, weight, IGF-1, IGF-binding protein (IGFBP)-3, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), thyroid function, peak GH after stimulation, pubertal status, were collected respectively. Zinc deficiency and hypothyroidism can result in growth retardation or short stature, both thyroid function and zinc concentrations were collected before both conditions were treated. Some patient presented with a spontaneous start of puberty, and the pubertal status (Tanner stage for breast development) was assessed and documented breast development at Tanner stage 1 to 2.[18] Bone age was available within 1 months of the stimulation test. Body mass index (BMI) was calculated, and weight and height standard deviation scores (SDS) were calculated using Chinese Child Health Statistics standards.[15,16,19] Documentation of pituitary magnetic resonance imaging (MRI) and B-ultrasound of uterine and ovaries were available.

Growth Hormone Provocative Test

Priming with sex steroids in stimulation tests for the diagnosis of GHD remains controversial.[20] In mainland of China, the practice of sex hormone priming during GH stimulation hasn't been executed in clinical use in most paediatric centres including our hospital. All patients performed provocative tests with a combination of at least two of the following: arginine, levo-dopa or insulin to assess GH secretion: arginine (arginine 0.5 g/kg, maximum 30 g, iv over 30 minutes, with blood sampling every 30 minutes for 90 minutes); dopamine (levo-dopa 150-175 mg/m^{2}, maximum 250 mg, with subsequent blood sampling at 30, 45, 60, 90); insulin (fasting over 10 hours and routine insulin 0.1 U/kg, with blood sampling at 0, 15, 30, 60, and 90 minutes).

Cytogenetic Analysis

The cytogenetic findings were analysed in the medical biology and genetic laboratory of our hospital. The karyotype was determined as we reported previously.[21] The karyotypic descriptions were reported according to the International System for Human Cytogenetic Nomenclature recommendations (ISCN, 1995).

Assays

Serum GH levels were measured with a solid-phase, two-site chemiluminescent immunometric assay with analytical sensitivity of 0.01 µg/liter, intraassay coefficient of variation (CV) ranging from 4.1-6.5% (DPC America). Serum IGF-1 levels were also measured with an analytical sensitivity of 20 µg/liter, intraassay CV ranging from 3.1-4.9% (diagnostic systems laboratories America). IGFBP-3 levels were measured (diagnostic systems laboratories America) using immunometric assay with a lower limit of 0.4 mg/liter, intraassay CV of 5.1-12%.

Statistical Analysis

Results are described as mean±SD unless stated. Data that were not normally distributed were natural log transformed to approximate a normal distribution, this was required for peak GH and IGF-1 levels. Pearson's chi-square test was performed for categorical variables. Spearman's correlational analysis was used to identify the causative factors for height SD and other indexes. Statistical significance was defined as $P<0.05$. Statistical analysis was performed using SPSS16.0.

Results

Age and Karyotype

Sixty girls with TS performed provocative GH testing for short stature were included in this study. The mean age at diagnosis was 10.9±3.5 years (range 4.2-18.3 years). The age presented with short stature was 2.6 years (range 0.1-9.4 years), the duration of growth retardation was 8.3±3.7 years (1-17 years). A spontaneous start of puberty occurs in 20% (12/60) with TS, which presented with Tanner stage 2 of breast. Thirty-one cases had 45,X, which accounted for 51.7% of the total group. Nine cases had 45,X/46,XX, 6 cases had 45,X/46,X,i(Xq) and 6 cases 46,X,i(Xq); The other chromosome abnormalities included 2 cases of 46,X,Xp-, 2 cases of 45,X/46,r(X)(p22-q11), 2 cases of 45,X/47,XXX, 1 case of 45,X,ace+ and 1 case of 45,X /46,XY.

The Comparison of Clinical Features between Patients with Different Karyotypes

The patients were divided into two groups by their karyotypes: 45,X group and miscellaneous karyotypes (MK) group including 45,X/46,XX, 45,X/46,X,i(Xq) except for 45,X. There were no differences in age at diagnosis, weight, BMI, the height of their parents, basal LH and FSH levels, IGF-1 and IGFBP-3 levels between two groups, however, the height SDS at diagnosis were -4.13±1.44, -3.12±1.3 for 45,X and MK group respectively, which showed differences (P=0.014) (Table 1). The incidence of undetected ovaries (including both

unilateral and bilateral ovaries absence) in 45,X group was higher than MK group (33.3% vs. 12.5%, P=0.046). 11% and 17% have hypothyroidism and zinc deficiency in total group, however, there are no difference in the incidence of GHD, hypothyroidism and zinc deficiency between 45,X and MK group [10/31 (32.3%) vs. 13/29 (44.8%), P=0.368; 7/31 (22.6%) vs. 10/29 (34.5%), P=0.280; 5/31 (16.1%) vs. 6/29 (20.7%), P=0.739].

The Correlation of Birth Weight and the Indexes such as IGF-1, IGFBP-3, and GH Peak Values in Turner Syndrome

The mean birth weight of total patients was 2.90± 0.47 kg. There was no difference in birth weight between 45,X and MK group (2.90±0.59 kg vs. 2.88±0.30 kg, t=-0.16, P=0.873). Birth weight was positively related to height SDS and weight SDS(r=0.364 P=0.007; r=0.378, P=0.005) respectively among total patients. There were no correlations between birth weight of total patients and their BMI, IGF-1, IGFBP-3, height and other indexes, birth weight was positively related to basal serum PRL in 45,X group (r=0.541, P=0.004) (Table 2).

The IGF-1 was positively correlated to IGFBP-3 in total patients (r=0.548, P=0.000), 45,X group (r=0.551, P=0.002) and MK group (r=0.539, P=0.006). There was no correlation between height SDS of patients and GH peak values (r=-0.182, p=0.182), IGF-1 (r=-0.075, P=0.583) and IGFBP-3 (r=-0.019, P=0.891) for total patients, and GH peak values showed no correlation with IGF-1 and IGFBP-3 (r=-0.256, P=0.059; r=-0.249, P=0.057) either for total patients. The correlations between GH peak values and IGF-1, IGFBP-3 were further analysed in two subgroups, GH peak values showed no correlation with IGF-1 (r=-0.155, P=0.43) but negatively correlation with IGFBP-3 (r=-0.374, P=0.047) in 45,X group, however, GH peak values showed no correlation with IGFBP-3 (r=-0.104, P=0.612) but negatively correlation with IGF-1 (r=-0.409, P=0.038) in MK group.

Discussion

Age at Diagnosis

TS is associated with an astounding array of potential abnormalities. About half of the individuals with TS have a 45,X karyotype and 20-30% has mosaicism. 45,X karyotype accounted for 51.7% in our cohort, which was in accordance with the previous reports.[1] Adult height deficit in TS originates, in part, from growth retardation

in utero and throughout the first 3 years of life.[22] Girls with TS grew more slowly due to three principal factors: a slow growth rate of the infancy component, a slow growth rate at the onset of the childhood component, and delayed onset of the childhood component. TS girls born with intrauterine growth retardation exhibit growth failure as early as 1 year of age. Mean height SDS in full-term girls with TS fell from -0.68 at birth to -1.60 at 1 year, -1.80 at 2 years and -1.95 at 3 years.[22,23] The diagnosis of TS is often made too late, The mean age of our patients at diagnosis was 10.9 years old, which is later than that in developed countries and similar to some developing countries.[24,25] Early detection allows for the initiation of GH treatment and permits the clinician to counsel the family about the consequences of TS, such as an increased risk for cardiac and auditory abnormalities. Optimal GH treatment of short stature in TS requires early initiation with the highest safe dose in the first year.[26,27] The presence of less pronounced growth deficit and/or spontaneous pubertal signs in some cases may contribute to delayed clinical suspicion of TS. Paediatricians should consider the diagnosis of TS in any girl with unexplained failure to thrive or short stature, even in the first 3 years of life.

GH/IGF-1/IGFBP-3

Spontaneous secretion of GH in the patients with TS was lower than that of the short normal prepubertal girls. Pirazzoli reported that 44% of the TS patients showed GH responses to pharmacological tests <8 microg/l.[11] GHD occurred in 38.3% (23/60) among our TS patients, it is higher than other children presented with short stature, however, there was no correlation between height SDS and GH peak values, so growth impairment in TS is mostly not due to GHD. The estimation on the spontaneous and stimulated GH secretion in TS is equivocal because it is affected by secretion of estrogen. Decreased circulating levels of estrogen do not preserve GH secretion.[28] The diagnostic criteria for GHD of GH stimulation tests are currently based on arbitrary cut-offs that do not take into account the shifting baseline from the changing gonadal steroid milieu of puberty. In other hands, BMI affects stimulated GH peak. Higher BMI SDS may lead to overdiagnosis of GHD in children with short stature.[29] It is also necessary to consider BMI and the changing gonadal steroid milieu when interpreting the results of provocative GH tests in children with TS.

Table 1　The comparison of clinical features between patients with different karyotype

	Age at diagnosis (year)	Duration of short stature (year)	Height of patients (cm)	Height SDS	Weight (kg)	Weight SDS	BMI of patients (kg/m²)	Height of father (cm)	Height of mother (cm)	Basal LH mIU/ml	Basal FSH mIU/ml	Basal PRL ng/ml	GH Peak Value	Serum IGF-1 ng/ml	Serum IGFBP-3 ng/ml
45,X group (n=31)	11.4±3.6	8.4±3.6	119.1±10.7	-4.13±1.44	25.1±6.5	-1.53±0.77	17.37±2.49	168.1±6.2	157.6±3.7	8.67	54.53	16.62	11.9	176.7±93.1	4222.6±1499.9
Other group (n=29)	10.6±3.6	8.1±3.9	123.5±18.6	-3.12±1.3	30.8±26.8	-1.28±0.81	18.56±7.33	170.0±4.4	156.5±5.2	6.23	36.62	18.02	11.9	181.3±88.3	4008.2±1749.8
t	0.831	0.362	-1.121	-2.542	-1.157	-1.164	-0.843	-1.354	0.963	1.114	1.60	-0.448	0.038	-0.187	0.486
P	0.409	0.719	0.267	0.014*	0.252	0.249	0.403	0.181	0.34	0.27	0.115	0.658	0.97	0.853	0.563

Data presented as mean±SD or median; *represents P<0.05 for between group difference.

SDS; standard deviation score; BMI: body mass index; LH: luteinizing hormone; FSH: follicle stimulating hormone; PRL: prolactin; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor-binding protein-3

Table 2　The correlation of birth weight and the indexes such as IGF-1, IGFBP-3 and GH peak values in Turner syndrome

	Height of father (cm)	Height of mother (cm)	Height SDS of patients	Weight SDS of patients	BMI of patients	Basal serum LH	Basal serum FSH	Basal serum PRL	GH peak value	Serum IGF-1	Serum IGFBP-3
Total cases	r=0.099 P=0.483	r=0.061 P=0.68	r=0.364 P=0.007*	r=0.378 P=0.005*	r=0.131 P=0.349	r=0.085 P=0.539	r=0.045 P=0.745	r=0.188 P=0.172	r=0.083 P=0.556	r=-0.014 p=0.921	r=-0.125 p=0.385
45,X group	r=0.067 P=0.747	r=0.101 P=0.624	r=0.424 P=0.028*	r=0.48 P=0.075	r=0.107 P=0.601	r=0.009 P=0.996	r=0.047 P=0.817	r=0.541 P=0.004*	r=0.186 p=0.352	r=0.09 p=0.608	r=-0.25 p=0.227
MK group	r=0.159 P=0.437	r=-0.014 P=0.945	r=0.365 P=0.069	r=0.489 P=0.010*	r=0.243 P=0.231	r=-0.217 P=0.297	r=-0.242 P=224	r=-0.152 P=0.392	r=-0.181 p=0.365	r=-0.18 p=0.399	r=-0.033 p=0.88

*represents P<0.05.

IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor-binding protein-3; GH: growth hormone; SDS: standard deviation score; BMI: body mass index; LH: luteinizing hormone; FSH: follicle stimulating hormone; PRL: prolactin; MK: miscellaneous karyotypes

In children and adolescents with GHD, the primary role of GH is to promote linear growth. After achieving their final adult height, GH replacement in adults with persistent GHD prevents metabolic imbalances.[30] Growth hormone replacement therapy results in improvements in body composition, dyslipidemia and bone mineral density in adults with GHD.[31] The metabolic derangements And Congenital Cardiovascular l defects such as aortic dilation in TS patients with childhood-onset GHD should be focused on when being treated with GH.

There were no differences in the height of their parents, IGF-1, IGFBP-3, and basal LH, FSH, PRL levels between 45,X and MK group. However, the height-SDS at diagnosis showed differences (-4.13±1.44 vs. -3.12±1.3 P=0.014) between 45,X and MK group, and there was no correlation between height SDS and GH peak values. Hence karyotypes especially 45,X may be one of the main factors impacting on height SDS. It also indicates the growth response can be poor in girls with TS. First, previous studies showed there exists a certain extent of GH/IGF-1 insensitivity and GH insensitivity resulting from IGF-1 insensitivity is supposedly due to defects in the SHOX gene in TS.[6] Second, altered IGF-1 activity, because of reduced bioavailability and/or reduced sensitivity, could contribute to the need for high GH doses in TS and for the poor response to GH in some girls with TS.[32] IGF-1 levels should be monitored routinely during long-term GH therapy in girls with TS.

Peak GH was negatively correlated with IGFBP-3 in 45,X patients and negatively correlated with IGF-1 in MK patients. The reasons for the conflicting observations are not clear. First, although the serum IGF-1 level is mainly dependent on the GH level, IGF-1 responsiveness to GH may be modulated by other factors, including gender, age, nutrition, body composition, and previous therapy, and the causal relationship is obscure. Second, the regulatory interaction by estrogens on GH may occur at many levels: secretion, clearance, and action. IGF-1 circulates almost entirely as a ternary complex bound to IGFBP-3 and the acid labile subunit (ALS). In contrast to IGF-1 and ALS, IGFBP-3 is synthesized in Kupffer cells rather than in hepatocytes and could be regulated differently by estrogens.[33] The incidence of undetected ovaries (including both unilateral and bilateral ovaries absence) in 45,X group was higher than MK group (33.3% vs. 12.5%, P=0.046). We supposed that the estrogen concentration could be higher in MK group than 45,X group.

Birth Weight

Long-term relationship between low birth weight for gestational age and growth in adolescence was found. Girls with TS who had a normal (for gestational age) body mass at birth, attain a higher stature than TS girls born with deficient body mass.[34] The mean birth weight of total patients was 2.90±0.47 kg, which was lower than healthy newborns, and was similar to other TS population.[35] LBW was observed in 23% of girls with TS.[36] Individuals with SHOX deficiency have variable degrees of growth impairment. It is noteworthy that the degree of short stature with haploinsufficiency for the SHOX gene is not as severe as that in TS patients, which suggested that haploinsufficiency for additional genes located on the X-chromosome also contribute to the growth retardation in TS.[37] LBW in TS girls may arise from a partial dysfunction of genes on the X-chromosome involved in the control of fetal growth. Birth weight was positively related to their height SDS and weight SDS (r=0.364, P=0.007; r=0.378, P=0.005 respectively) in patients with TS. Therefore, it is necessary to investigate the underlying mechanism of association between low birth weight and adulthood short stature in TS patients.

In conclusion, there is an association between karyotype and height SDS and birth weight have important impact on height SDS in TS girls performed GH provocative tests for short stature. Our study has some limitations. It used a cross-sectional design with a small number of young patients. We did not correct for other possible contributors to the height, such as nutrition, physical inactivity, socioeconomic status. Long-term follow-up studies of larger groups are needed to understand the changes in metabolic derangement after childhood in TS patients.

Declaration of Conflicts of Interest

The authors hereby declare that there is either: (a) no conflict of interest that would prejudice its impartiality; or (b) a potential conflict of interest that is fully declared within the text of the article.

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