CASE REPORT

Longitudinal auxological study in a female with SHOX (short stature homeobox containing gene) haploinsufficiency and normal ovarian function

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Abstract

Objective: To report on auxological data in the combination of SHOX (short stature homeobox containing gene) haploinsufficiency and normal ovarian function.

Design: Longitudinal auxological study in a 14 year 9 month old Japanese girl with Léri–Weill dyschondrosteosis accompanied by mesomelic short stature, who had a submicroscopic pseudoautosomal deletion involving SHOX, and pubertal development of an almost average tempo.

Methods: Auxological data were assessed by the age-matched standards for Japanese females.

Results: The standard deviation scores (SDSs) for height, leg length (LL), and arm span remained below the normal range from childhood and worsened during puberty, whereas those for sitting height (SH) remained within the normal range and stayed almost constant throughout the observation period. Consequently, the SDSs for SH/LL ratio remained above the normal range from childhood and deteriorated during puberty. The decreased pubertal height gain was caused by a diminished pubertal height spurt and abrupt growth cessation shortly after menarche. The SDSs for hand length and palm length remained within the normal range but decreased during puberty, and those for head circumference remained within the normal range and stayed almost constant throughout the observation period.

Conclusions: The results suggest that, in individuals with SHOX haploinsufficiency and normal ovarian function, auxological abnormalities related to mesomelia are evident from childhood and worsen further during puberty because of the skeletal maturing effects of ovarian estrogens.

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Introduction

SHOX (short stature homeobox containing gene) cloned from the short arm pseudoautosomal region (PAR1) of the human sex chromosomes has been shown to be relevant to the development of specific features in Turner syndrome. Clinical studies in patients with SHOX mutations or pseudoautosomal microdeletions involving SHOX as the sole disease gene have indicated that SHOX haploinsufficiency causes not only short stature but also Turner skeletal features such as short metacarpals, cubitus valgus, and Madelung deformity characteristic of Léri–Weill dyschondrosteosis (LWD) (1–4). Since skeletal features are more severe in females than in males and become obvious with puberty, it has been suggested that gonadal estrogens exert a maturational effect on skeletal tissues that are susceptible to unbalanced premature fusion of growth plates because of SHOX haploinsufficiency, facilitating the development of skeletal lesions and resultant growth deficiency in a female-dominant and pubertal tempo-dependent fashion (2).

To our knowledge, however, longitudinal growth data remain poor in individuals with SHOX haploinsufficiency and normal gonadal function. In particular, there has been no report describing detailed long-term auxological data including body proportion. Here, we report the longitudinal auxological data in a female with SHOX haploinsufficiency and normal ovarian function, and discuss the characteristics of the auxological findings.

Case report

This Japanese female was born at 40 weeks of gestation after an uncomplicated pregnancy and delivery.
At birth, her length was 50.0 cm (+0.2 S.D.) and her weight was 3.500 kg (+1.3 S.D.). The parents were non-consanguineous and clinically normal.

At 5 years and 1 month of age, she was seen because of short stature. Her height was 95.1 cm (−2.5 S.D.) and her weight was 16.2 kg (−0.6 S.D.). She exhibited mild cubitus valgus and mesomelic appearance. Endocrine studies for short stature were normal. At 8 years and 9 months of age, a bone survey was performed including radiographs of the hands and forearms, showing bilateral decreased carpal angles, angulation of the distal radii, and shortening and curvature of radii indicative of LWD. On the last examination at 14 years and 9 months of age, she measured 140.7 cm (−3.0 S.D.), weighed 50.6 kg (−0.1 S.D.), and manifested moderate cubitus valgus, genu valgum, and mesomelia as the clinically recognisable Turner skeletal features.

Methods

Cytogenetic and molecular studies

After obtaining informed consent, blood samples were taken from the patient and the parents. Chromosome analysis was performed on 50 peripheral lymphocytes by G-banding. Fluorescence in situ hybridization (FISH) analysis was carried out for lymphocyte metaphase spreads with probes for the Xp/Yp telomere region (2), SHOX (−500 kb from the Xp/Yp telomere) (2), and MIC2 (~2500 kb from the Xp/Yp telomere) (5) on the PAR1, together with a probe for the Xq/Yq telomere region (Vysis, http://www.vysis.com/) used as an internal signal control. The probe for the Xq/Yq telomere region was labeled with biotin and detected by avidin conjugated to fluorescein isothiocyanate, and the remaining probes were labeled with digoxigenin and detected by rhodamine anti-digoxigenin.

Microsatellite analysis was also performed for the marker SHOX 5′UTR CA repeat (6). In brief, 0.3 μg leukocyte genomic DNA was amplified by polymerase chain reaction with a fluorescently labeled forward primer and an unlabeled reverse primer, and the size of the PCR products was determined on an ABI PRISM 310 autosequencer using GeneScan. The primer sequences were as reported previously (6).

Auxological studies

Statural growth was evaluated by the longitudinal height standards for Japanese girls (7). Sitting height (SH), leg length (LL, height minus SH), SH/LL ratio, arm span (AS), hand length (HL), palm length (PL), and head circumference (HC) were assessed by the age-matched standards for Japanese girls (8, 9).

Target height (TH) and target range (TR) were obtained from the equations of Ogata et al. (a modified Tanner’s equation for the Japanese) (10).

Maturational assessment

Bone age (BA) was determined by the TW-2 method standardized for the Japanese (11). Pubertal stage was evaluated by the classification of Tanner (12). Pubertal tempo and menarchial age were assessed by the reference data for Japanese girls (13).

Results

Cytogenetic and molecular studies

The karyotype was normal in the patient and in the parents. FISH analysis showed that the patient had a heterozygous submicroscopic deletion distal to MIC2 involving SHOX and the Xp/Yp telomere region, whereas the parents had no deletion in the PAR1. Microsatellite analysis for the marker SHOX 5′UTR CA repeat revealed a 149 bp peak in the patient, 141 bp and 149 bp peaks in the mother, and a 153 bp peak in the father, demonstrating that the de novo SHOX deletion of the patient occurred in the paternally derived X chromosome.

Auxological studies

The data are summarized in Table 1, together with standard deviation scores (SDSs). The patient’s growth followed the −2 S.D. growth curve before puberty, and showed a downward growth shift with puberty (Fig. 1, left panel). Her nearly final height was unequivocally below her TH (162 cm, 0.9 S.D.) and TR (154 ~ 170 cm, −0.7 ~ +2.5 S.D.). The height velocity was in the low-normal range before puberty, slightly increased with puberty, and abruptly decreased shortly after menarche.

Throughout the observation period from childhood to puberty, the SDSs for height, LL, SH/LL ratio, and AS remained outside the normal range, whereas those for SH, HL, PL, and HC remained within the normal range (Fig. 1, right panel). Furthermore, the SDSs for SH remained almost constant, but those for LL slightly increased just before puberty and greatly decreased during puberty; consequently, the SDSs for the SH/LL ratio slightly decreased just before puberty and markedly increased during puberty. The SDSs for AS, though the data were scanty, decreased during puberty. The SDSs for HL and PL slightly decreased during puberty. The SDSs for HC remained almost constant.

Maturational assessment

The data are shown in Table 1 and Fig. 1 (left panel). The patient’s pubertal development progressed at a roughly average tempo for Japanese girls. Menarche occurred at 12 years and 6 months (reference data in normal Japanese girls: 12.25 ± 1.25 years) and was
Table 1  Auxological and Maturational data of the subject.

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SH: sitting height; LL, leg length; AS, arm span; HL, hand length; HC, head circumference; SDS, standard deviation score; ND, not determined because of lack of reference data for Japanese girls.

* Tanner stage in normal Japanese girls (years): B2, 10.0±1.4; B3, 11.6±1.5; B4, 13.3±1.5; B5, 14.2±1.2; P2, 11.7±1.6; P3, not available; P4, 13.9±1.0; P5, not available (a considerable number of normal Japanese females do not reach the P5 stage) (13 and our unpublished observation). Menarchial age of this girl: 12.5 years (reference data in Japanese girls: 12.25±1.25 years) (13).
followed by regular menses. BA was comparable to her chronological age (CA) before puberty, and advanced more rapidly than CA during puberty.

**Discussion**

This girl had a combination of SHOX haploinsufficiency and normal ovarian function. Since she manifested pubertal development of an almost average tempo for Japanese girls, her phenotype would serve to define the standard auxological characteristics in females with this combination.

The SDSs for height, LL, SH/LL ratio, and AS remained outside the normal range from childhood and worsened during puberty, whereas those for SH and HC remained within the normal range and stayed almost constant throughout the observation period. The distribution of affected and unaffected regions is consistent with the SHOX expression pattern, because SHOX expression is detected in the developing bones in the forearms and shanks as well as in the first and second pharyngeal arches, and is undetected in the vertebral and cranial bones (3). Similarly, the deterioration of mesomelic appearance during puberty is compatible with normal ovarian function in this girl, because the combination of SHOX haploinsufficiency and gonadal estrogens has been suggested to exert a synergic effect on skeletal maturation including growth plate fusion (2, 4). Furthermore, the present study suggests that the small pubertal height gain is due to a diminished pubertal height spurt and abrupt growth cessation shortly after menarche. Although it remains to be determined why mesomelia transiently ameliorated before puberty, this may be related to the initiation of the growth spurt, as indicated by the growth chart for height velocity.

The SDSs for HL and PL remained within the normal range but decreased during puberty. This may be explained by assuming that SHOX expression is relatively weak in the acral regions. In support of this, SHOX expression in human embryos is less evident in the acral regions than in the forearm and shank regions (3), although short metacarpals in Turner syndrome argue for SHOX expression in the metacarpal bones. It is possible, therefore, that the acral growth is fairly well preserved before puberty but is somewhat impaired during puberty because of accelerated skeletal maturation by ovarian estrogens. This notion would also explain why BA was comparable to CA before puberty and progressed more rapidly during puberty than CA.

The auxological characteristics of this girl are grossly reminiscent of those of non-Japanese Turner females reported in the literature (14–16). However, mesomelia appears to be more severe in this girl. This would primarily be due to the normal ovarian function of this girl, although ethnic difference would also be involved in the difference in the severity of mesomelia. By contrast, SH, HL, PL, and HC appear to be more severely impaired in Turner females. In this context, it has been postulated that, in Turner syndrome, haploinsufficiency of an Xp-Yp homologous
lymphogenic gene causes lymphatic hypoplasia, leading to lymph fluid stasis and resultant distended lymphatics and lymphedema (17). Since distended lymphatics and lymphedema should exert a compressive effect on tissues/organs adjacent to the lymphatics, they have been regarded not only as the major cause for the appearance of soft tissue and visceral Turner stigmata (17), but also as the modifying factor for the development of faciocervical skeletal features as well as cubitus valgus and short metacarpals (18, 19). Such a compressive effect on the developing skeletal tissues may be relevant to the more compromised growth of SH, HL, PL, and HC in Turner syndrome. In summary, the results suggest that SHOX haploinsufficiency causes auxological abnormalities related to mesomelia from childhood, and that ovarian estrogens further worsen the auxological abnormalities during puberty by facilitating skeletal maturation. Further studies in similarly affected individuals will permit a better clarification of auxological characteristics in SHOX haploinsufficiency associated with normal ovarian function.

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