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Longitudinal Observation of a Patient with Leri-Weill Dyschondrosteosis and SHOX Haploinsufficiency

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Abstract. Haploinsufficiency of the short stature homeobox-containing (SHOX) gene causes Turner skeletal features, a certain proportion of idiopathic short stature and Leri-Weill dyschondrosteosis (LWD). Here we report a Japanese female with LWD. Her physical growth, skeletal deformity, and endocrine status were recorded longitudinally. She exhibited a constant growth rate (average + 6.2 cm/yr) from 6 to 9 yr old, followed by a downward shift at 10 yr old. Her final height was 135 cm (−4.4 SD for an adult female) and weight was 50.5 kg (−0.3 SD) at 12 yr and 10 mo old. Mesomelia and cubitus valgus were noticed from 2 yr old, and metaphyseal lucency and epiphyseal hypoplasia of the medial side of the distal radius were detected at 6 yr old. Madelung deformity was obvious at 10 yr old, when menarche occurred. Fluorescence in situ hybridization (FISH) analysis demonstrated a single copy of the SHOX gene. The short stature of the patient was thought to be exaggerated by the combination of SHOX haploinsufficiency and relatively early puberty.

Key words: short stature homeobox-containing (SHOX) gene, haploinsufficiency, Leri-Weill dyschondrosteosis, transient neonatal hyperthyroidism

Introduction

The haploinsufficiency of the short stature homeobox-containing (SHOX) gene causes Turner skeletal features (1,2), a certain proportion of idiopathic short stature (3, 4) and Leri-Weill dyschondrosteosis (LWD) (OMIM127300) (5, 6). The SHOX gene was cloned from the

pseudoautosomal region of the sex chromosome (Xp22 and Yp11.3) (3). It is exclusively expressed in the first and second pharyngeal arches and in the developing distal limb bones of the human embryo (2). LWD is an autosomal dominant form of mesomeric dysplasia first described by Leri and Weill in 1929 (7). Patients with this condition demonstrate short stature due to shortening of the lower legs and Madelung deformity of the forearms. While inter- and intrafamilial phenotypic heterogeneity is a frequent finding, phenotypic manifestations are generally more severe in females (8). Although a number of reports have been published on SHOX haploinsufficiency, the

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number of longitudinal follow-up studies is limited, and its endocrine status has not been fully clarified. Here, we report the case of a 12 yr-old Japanese female with LWD and transient neonatal hyperthyroidism. We assessed her outcome with regard to physical growth, skeletal deformity, and endocrine status.

Case Report

The patient was vaginally delivered at 37 wk of gestation after an uncomplicated pregnancy with a weight of 2628 g (-0.5 SD), a length of 46.5 cm (-0.7 SD) and an occipitofrontal circumference of 35.0 cm ($+1.3$ SD). Her mother developed hyperthyroidism before bearing children and was taking 100 mg dose of propylthiouracil at the period of delivery. As tachycardia, goiter, and exophthalmos developed in the baby, treatment with methimazole, Lugol solution, and propranolol were started at 6 d old. Thyroid function became normal at 15 d old, and treatment with methimazole was continued without any complications for 4 mo. Although the child's goiter initially regressed at 4 mo old, both anti-TgAb and anti-McAb reappeared with enlargement of the thyroid gland at 8 yr old. Her height was 66.4 cm (-2.5 SD), and her weight was 7660 g (-1.3 SD) at one year old. Her height gradually caught up to -2.0 SD at 3 yr old, and she continued to grow along the -2 SD growth curve. Growth charts of the patient and her elder sister are shown in Fig. 1. Her height gradually rose above -2 SD from 6 yr old. She exhibited a constant growth rate (average $+6.2$ cm/yr) from 6 to 9 yr old, followed by a downward shift at 10 yr old. She was noticed to have breast development of Tanner stage 2 at 9 yr old. Menarche occurred at 10 yr and 10 mo old, and was followed by regular menses. Although bone age estimated by the TW-2 method standardized for Japanese was comparable with chronological age from infancy to 3 yr old, it was noticed to be advanced for chronological age after 6 yr old, and reached an adult level at 11 yr old (Fig. 1).

Mesomelia and cubitus valgus were noted from 2 yr old. Bilateral metaphyseal lucency and epiphyseal hypoplasia of the medial side of the distal radius were first detected at 6 yr old. Madelung deformity was noted at 10 yr old. The area of metaphyseal lucency and Madelung deformity progressed with pubertal development. Psychomotor and intellectual developments were normal.

Detailed clinical examinations, including anthropometrical measurement, endocrinological survey and radiological examination of the patient were conducted at 12 yr and 10 mo old. Her height was 135 cm (-4.4 SD for an adult female) and weight was 50.5 kg (-0.3 SD); the obesity index was 66%. She exhibited a mesomelic appearance, cubitus valgus and mildly high arched palate. She had neither webbed neck, short 4th metacarpals nor scoliosis. Her arm span was 123 cm, indicating relatively short arms. Subischial leg length was 60 cm, and sitting height was 81 cm. The upper and lower segment ratio was 1.25, indicating relatively short lower limbs. Wrist movements and supination of the elbows was without limitation (R 190° , L 190°), but pronation of the elbows was extremely limited (R 10° , L 20°). She had neither pain nor inconvenience when using her extremities. Radiographs of her hands and forearms showed bilateral decreased carpal angle formed by tangents of the scaphoid-lunate and triquetrum-lunate peripheries, shortening and curvature of the radius suggestive of Madelung deformity (Fig. 2). Growth plates of the hands had already fused. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DEXA) (LUNAR, DPX-L). BMD of the total body was 1.076 g/cm², and BMD of the lumbar spine (L2-4) was 1.101 g/cm², which was comparable to that of other girls aged 14 yr old (9). Body fat distribution estimated by the DEXA scan was as follows: arms 50%, legs 44%, trunk 38%, total body 42%.

An endocrinological survey to detect the cause of growth failure was performed, but no obvious abnormalities were found. Thyroid function tests

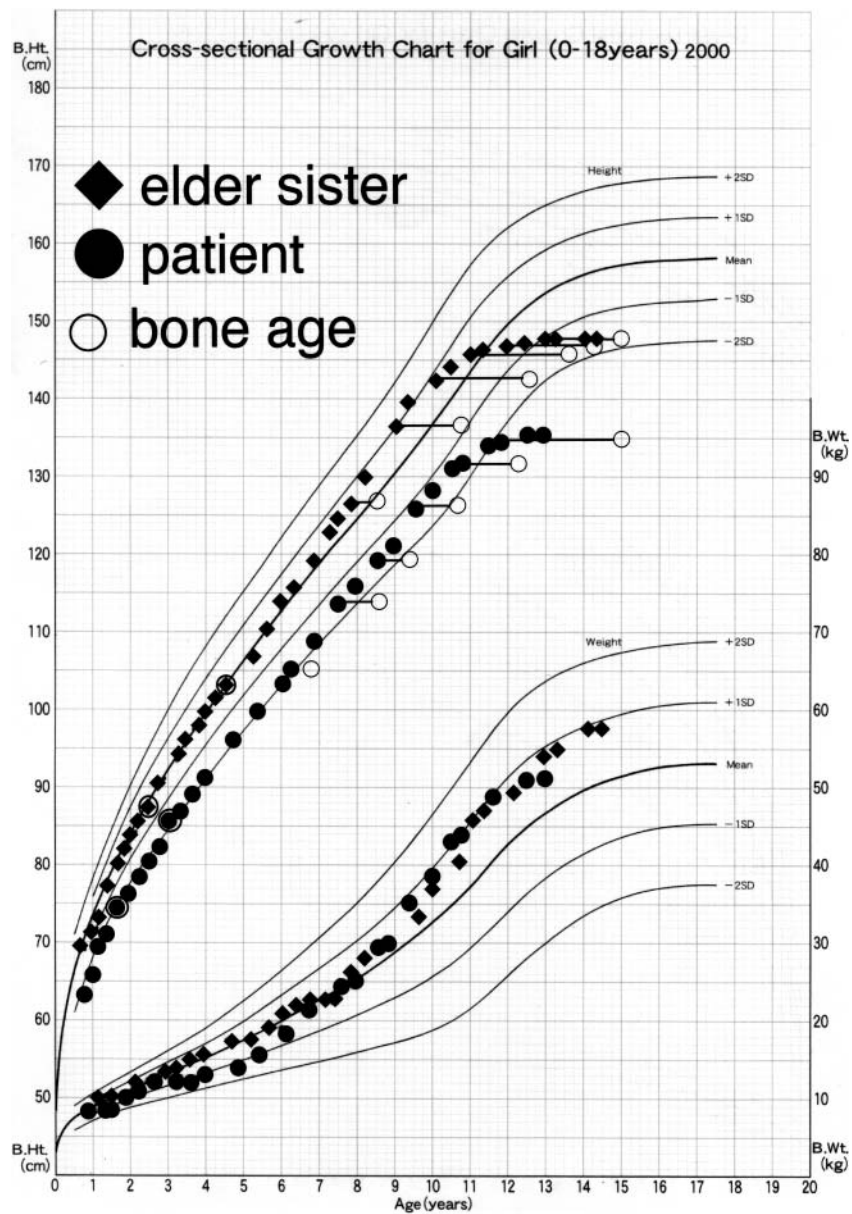


Fig. 1 Growth chart of the patient and the elder sister. Filled circles and diamonds indicate height and weight, and open circles indicate bone age estimated by the Japanese TW-2 method.

were as follows: TSH $2.33 \mu\text{U}/\text{ml}$, free T4 $1.2 \text{ ng}/\text{dl}$, free T3 $3.0 \text{ pg}/\text{ml}$, TRAb $<1.4\%$, TgAb $13.7 \text{ IU}/\text{ml}$, McAb $\times 6400$. Insulin-like growth factor-1 (IGF-1) was $639 \text{ ng}/\text{ml}$ (normal range; $370\text{--}896 \text{ ng}/\text{ml}$) and IGF-binding protein 3 (IGFBP-3) was $4.42 \mu\text{g}/\text{ml}$ (normal range; $2.75\text{--}5.15 \mu\text{g}/\text{ml}$). Basal serum

FSH, LH and E2 levels were $7.7 \text{ mIU}/\text{ml}$, $6.0 \text{ mIU}/\text{ml}$ and $48 \text{ pg}/\text{ml}$, respectively. The insulin level was mildly elevated to $20 \mu\text{IU}/\text{ml}$, when the fasting plasma glucose level was $91 \text{ mg}/\text{dl}$. HbA1c was 4.5% .

Chromosomal analysis using peripheral blood



Fig. 2 X-ray of the left arm at 12 yr old. The X-ray showed decreased carpal angle and Madelung deformity.

lymphocytes demonstrated an excess band on the terminal short arm of the X chromosome (Xp22.3). FISH analysis was performed for SHOX and CSF2RA at the positions ~500 kb and ~1.5 Mb from the Xp/Yp telomere, respectively. Informed consent was obtained from the parents. It showed that the abnormal X chromosome was negative for SHOX and positive for CSF2RA. This demonstrated that the aberrant X chromosome had a partial deletion of the pseudoautosomal region distal to CSF2RA. Furthermore, G-banding

analysis indicated that the extra chromosomal material attached onto the abnormal X chromosome was derived from a satellite chromosome with no significant biological effect. Taken together, it is assumed that the patient has SHOX haploinsufficiency, and is free from other genetic abnormalities reported in Xp deletions.

The patient's father was 163 cm tall (-1.3 SD), the mother was 153 cm tall (-1.0 SD), and the mother's menarche occurred at 12 yr old. Her parents were unrelated, and they had no definitive

physical abnormalities. The patient's elder sister, who was 14 yr and 11 mo old, had a final height of 147 cm (-2.1 SD for an adult female), weight of 58 kg ($+0.7$ SD), and arm span of 150 cm. After transient hyperthyroidism during the infantile period, her thyroid function stabilized within normal ranges without medication. Anti-TgAb and anti-McAb reappeared with enlargement of the thyroid gland. She was noticed to have breast development of Tanner stage 2 at 7 yr old, and menarche occurred at 9 yr and 10 mo old. She had no abnormalities on radiographs of her hands and forearms. The karyotypes of her parents and elder sister were normal.

Discussion

We described a 12-yr-old female with LWD and SHOX haploinsufficiency. This patient exhibited a characteristic growth pattern (Fig. 2). She showed a constant growth rate with no apparent pubertal growth spurt. Relatively early maturation of pubertal development and relatively rapid pubertal bone age progression were observed.

Recently, Binder *et al.* reported that auxology was a valuable instrument for clinical diagnosis of SHOX haploinsufficiency in Dutch school-age children with an unexplained short stature (10). They suggested that the likelihood of the presence of a SHOX gene mutation in Dutch school-age children, whose height-adjusted extremities to trunk ratio (calculated as the sum of arm span and subischial leg length, divided by sitting height) was less than $1.95 + 1/2$ height (m). In our case the height-adjusted extremities-trunk ratio $[(123 + 60) / 81 = 2.3]$ was smaller than the cut off point $[1.95 + (1.35/2) = 2.6]$, satisfying their criteria. Since this criterion is based on Dutch children, it might not be directly applicable to Japanese children. More data from Japanese patients with SHOX haploinsufficiency should be collected. Radiological analysis is also suggested to be useful; the lucency in the ulnar border of the distal radius is a very early and characteristic sign of wrist

dysplasia attributable to LWD (10). Metaphyseal lucency and epiphyseal hypoplasia of the medial side of distal radius were demonstrated at 6 yr old in the present case.

The SHOX gene normally seems to function as a promoter of linear growth and a repressor for growth plate fusion, and SHOX haploinsufficiency decreases adult height by about 12 cm (11). Estrogen has been shown to accelerate the programmed senescence of the growth plate, causing earlier fusion (12). The height deficit of the patient compared to her mid parental height (151.5 cm) was 16.5 cm, which might be due to SHOX haploinsufficiency combined with early pubertal maturation. Her elder sister, also demonstrated transient neonatal hyperthyroidism, manifested early pubertal development and short stature. Her menarche occurred at 9 yr and 10 mo old, which was one year earlier than the patient. The difference in adult height between the patient and her elder sister was 12 cm, and it seems to be due to SHOX haploinsufficiency and timing of puberty.

Schiller *et al.* pointed out that an athletic habitus seems to be frequent in LWD, and MRI demonstrated that this habitus was due to true muscular hypertrophy (8). In our case, skeletal deformity and obesity tended to be more obvious and progressed with pubertal development. We investigated her % body fat using DEXA scan, and showed a tendency towards excessive fat deposition in the extremities rather than the trunk.

We conclude that SHOX haploinsufficiency is a phenotypically heterogeneous disorder, and attention should be directed to auxological data and radiological analysis when examining female patients with short stature. Further investigation of pathophysiology and prognosis is required to improve management of this syndrome.

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