Metabolic syndrome coexists with adult Léri–Weill dyschondrosteosis: A case report

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INTRODUCTION
Léri–Weill dyschondrosteosis (LWD; OMIM #127300) is usually caused by haploinsufficiency of the short stature homeobox-containing gene (SHOX), which is located in the pseudoautosomal region 1 of the sex chromosomes, with the classic clinical triad of short stature, mesomelia and Madelung deformity1,2. Besides the aforementioned classic triad, individuals with LWD also have other features, such as hypertrophy of calf muscles, short fourth metacarpals, increased carrying angle of the elbow, high-arched palate, scoliosis and increased body mass index (BMI)2. Relatively shorter legs and shorter stature due to shorter legs are believed to increase the risk of overweight, cardiovascular disease (CVD) and diabetes3. The SHOX gene is involved in skeletal abnormalities in Turner syndrome (TS), which is caused by an X chromosome abnormality (including SHOX gene)4. However, unlike TS, there are very few metabolic disorders reported in LWD patients, despite LWD patients also having short stature and high BMI.

Here, we report a case of a woman with LWD caused by a heterozygous mutation of the start codon of the SHOX gene. She also had type 2 diabetes, hypertension, dyslipidemia and hypothyroidism caused by autoimmune thyroid disease. This suggests that LWD patients could have metabolic diseases as well, and we should be aware of this for early prevention.

CASE REPORT
A 50-year-old woman with type 2 diabetes, blood hypertension, dyslipidemia and hypothyroidism was referred to Department of Endocrinology and Metabolism, First Hospital of China Medical University, Shenyang, China. She had an 8-year history of type 2 diabetes and hypothyroidism, and have been followed up in the endocrine clinic. She did not have ketoacidosis in her history of diabetes. She went through menopause at the age of 49 years. Her BMI was 30.7 kg/m² at the onset. However, short stature, mesomelia and Madelung deformity were not noticed until this visit. Four members of her family, including her mother, had similar characteristics of mesomelia and Madelung deformity, but the other two male family members’ height was relatively normal. Her daughter was aged 24 years with normal height. The Hospital Ethics Committee of the First Hospital of China Medical University approved the study. The patient and her family provided written informed consent for publication of their data.

The proband’s height was 151 cm, sitting height : height ratio was 0.556, interphalangeal distance was 133 cm, arm span : height ratio was 0.88, weight was 74 kg, BMI was 32.45 kg/m² and blood pressure was 140/90 mmHg. The proband’s appearance characteristics are shown in Figure 1a, showing the shortening of the radius and Madelung’s deformity of the wrist.

Laboratory investigations are shown in Table 1, showing the characteristics of type 2 diabetes mellitus, hypercholesterolemia and a slightly lower thyrotropin-releasing hormone. An oral
glucose tolerance test was carried out during metformin treatment. Thus, the insulin response seemed to be modified by this treatment. Islet autoantibodies including glutamic acid decarboxylase and insulin autoantibody were tested and shown to be normal in this patient. A forearm roentgenogram suggested Madelung’s deformity, and manifested as a bilateral shortening and bowing of the radius, distal dislocation of the ulna (Figure 1b), wedged carpal bones and decreased carpal angle. Color Doppler ultrasound showed that the thyroid gland was slightly small, with a left lobe nodule of 0.59 × 0.45 cm (thyroid imaging reporting and data system 4a). The color Doppler ultrasound of the carotid artery showed sclerotic change with carotid intima-media thickness of 1.5 mm on the left and 1.1 mm on the right.

Genomic deoxyribonucleic acid was extracted from the peripheral blood of the proband and her family members. Multiplex ligation-dependent probe amplification was carried out with a SALSA MLPA P018-E1 SHOX kit (MRC-Holland, Amsterdam, the Netherlands). No deletions were found through the multiplex ligation-dependent probe amplification analysis. Sanger sequencing of SHOX-coding exons showed the heterozygous missense variant c.2T>C in exon 2, resulted in a heterozygous missense mutation with methionine to be replaced by threonine (Figure 1c). The same variant was found in the other three family members (Figure 1d). This M1T mutation has been reported in a case of Calabrian girl with LWD with a severe phenotype and growth retardation5.

Based on diet control and exercise, metformin 0.5 g three times daily, acarbose 50 mg three times daily, canagliflozin 100 mg once daily, amlodipine 2.5 mg once daily, atorvastatin 20 mg once daily and aspirin 100 mg once daily were recommended for the treatment of type 2 diabetes, hypertension, dyslipidemia and antiplatelet therapy. For the treatment of hypothyroidism, the dosage of levothyroxin was reduced from 87.5 to 75 μg once daily.

Figure 1 | Clinical characteristics and gene sequencing results of the patient and her family members. (a) The stubby forearm of the proband showing a Madelung deformity. Compared with the arm of a normal person above, the patient’s forearm shows shortness, Madelung deformity of the wrist and enlarged carrying angle. (b) The forearm roentgenogram shows the shortening and bowing of the radius. (c) Electropherogram of the SHOX gene exon 2 sequence shows the thiamine (T)>cytosine (C) transition resulting in Met1Thr mutation. (d) Pedigree of the patient’s family with SHOX gene deficiency. Males and females are indicated by squares and circles, respectively. An affected individual is indicated by filled symbols. Deceased individuals are indicated by symbols with slashes. The proband is indicated by a black arrow. The height is indicated in the lower right corner (in cm).
Table 1 | Laboratory investigations

| Test          | Result   | Normal values |
|---------------|----------|---------------|
|               | Base     | 30 min after OGTT | 60 min after OGTT | 120 min after OGTT | 180 min after OGTT |
| PG (mmol/L)   | 9.81     | 12.47          | 16.69            | 20.24            | 19.32            | –             |
| INS (mlU/L)   | 9.92     | 9.31           | 26.45            | 29.47            | 31.72            | –             |
| CP (pmol/L)   | 946.5    | 1434.8         | 1779             | 2233.4           | 2546.3           | –             |
| HDL-c (mmol/L)| 1.00     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TRAb (IU/L)   | 16.97    | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| fT3 (pmol/L)  | 3.35     | 2.63           | 9.01             | 9.01             | 9.01             | –             |
| TSH (mIU/L)   | 0.2279   | 0.35–4.94      | 0.35–4.94        | 0.35–4.94        | 0.35–4.94        | –             |
| UA (umol/L)   | 290.0    | 0.91–19.05     | 0.91–19.05       | 0.91–19.05       | 0.91–19.05       | –             |
| LDL-c (mmol/L)| 5.20     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TC (mmol/L)   | 7.09     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TG (mmol/L)   | 1.82     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| HDL-c (mmol/L)| 1.00     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| UA (umol/L)   | 290.0    | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TSH (mIU/L)   | 0.2279   | 0.35–4.94      | 0.35–4.94        | 0.35–4.94        | 0.35–4.94        | –             |
| fT3 (pmol/L)  | 3.35     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TSH (mIU/L)   | 0.2279   | 0.35–4.94      | 0.35–4.94        | 0.35–4.94        | 0.35–4.94        | –             |
| fT3 (pmol/L)  | 3.35     | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| TRAb (IU/L)   | 16.97    | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| GAD (IU/mL)   | 9.5      | 0.91           | 0.91             | 0.91             | 0.91             | –             |
| IAA (IU/mL)   | 6.53     | 0.91           | 0.91             | 0.91             | 0.91             | –             |

CP, serum C-peptide; fT3, free triiodothyronine; fT4, free thyroxine; GAD, glutamic acid decarboxylase; HbA1c, hemoglobin A1c; HDL-c, high density lipoprotein cholesterol; IAA, insulin autoantibody; INS, serum insulin; LDL-c, low density lipoprotein cholesterol; PG, plasma glucose; TC, total cholesterol; TG, triglyceride; TRAb, thyrotropin-releasing hormone receptor antibody; TSH, thyrotropin-releasing hormone; UA, uric acid.

DISCUSSION

The SHOX gene is the most important gene involved in human growth. Haploinsufficiency of SHOX is an important cause of human short stature. It is estimated that it accounts for 10% of the pathogenic causes of short stature and 70–90% of the pathogenic causes of LWD. In addition to short stature and LWD related to SHOX gene defects, haploinsufficiency of the SHOX gene is also involved in the phenotypes of TS caused by X chromosome abnormalities. Homozygous deletions of SHOX can also lead to Langer mesomelic dysplasia (OMIM #249700) with more severe phenotypes. The SHOX mutation database (http://www.shox.uni-hd.de) collected 511 cases of SHOX mutation, including idiopathic short stature (51.7%), LWD (41.3%), Langer mesomelic dysplasia (2.2%) and TS (1%). The SHOX deficiency-related phenotype is more common and severe in females, with a female : male ratio of 4:1. LWD is usually recognized in childhood because of the typical triad, the delayed diagnosis of the present proband shows that the recognition ability of Chinese doctors for the triad of LWD needs to be improved; this is probably due to no case report of LWD in China so far. As growth hormone treatment can improve the final height and skeletal deformity of individuals with LWD, it is important to identify LWD in early childhood. The increase of the sitting height : height ratio and the decrease of the arm span : height ratio reflects the characteristics of LWD. The Rappold score (≥5 points) designed in combination with other clinical characteristics can well predict LWD caused by SHOX gene defects.

Haploinsufficiency of SHOX is caused by a heterozygous SHOX deletion (80–90% of affected individuals) or a SHOX heterozygous pathogenic variant (10–20% of affected individuals). In the present case, the SHOX gene mutation M1T was located in the starting codon of exon 2, caused by ATG (methionine) replaced by ACG (threonine). According to the Kozak motif (GCCAUGG), it is speculated that ACG can still initiate SHOX protein translation, but it greatly reduces the efficiency of translation, leading to haploinsufficiency of SHOX. M1T was reported in a Calabrian girl with LWD with the severe phenotype. This mutation was carried by four members of that family, but there was no obvious short stature in men, suggesting that the phenotype of the same mutation had variability even in the same family. Phenotypes of LWD patients are more severe in females, which seems to be associated with higher levels of estrogen.

Short stature and high BMI in adults are risk factors for impaired islet β-cell function, insulin resistance, type 2 diabetes and CVD. Although the clinical manifestation of haploinsufficiency of SHOX is short stature and high BMI, there is no report about the metabolic disorders of LWD patients caused by SHOX deficiency in the literature, which might be related to the limited numbers of adult cases. The occurrence of hypertension in SHOX-deficient girls with TS is hypothetically due to reduced circulating brain natriuretic peptide levels as a consequence of SHOX deficiency. The observation of more adult LWD cases is required to determine whether there is a higher probability of metabolic syndrome, including type 2 diabetes, hypertension and dyslipidemia.

The complete or partial absence of one copy of the X chromosome will usually result in autoimmune diseases and malignant diseases. However, the possibility of combining with these diseases should be low in the case of haploinsufficiency of SHOX caused by a point pathogenic variant without affecting...
other regions of the X chromosome. Autoimmune thyroid disease might just be a coincidence in the present LWD patient carrying a point mutation of the SHOX gene.

In conclusion, we report an adult LWD patient with metabolic syndrome due to a heterozygous mutation of the start codon of the SHOX gene. Clinicians should identify and treat LWD patients promptly according to the LWD triad and Rappold score, and pay attention to whether adult LWD patients are at risk of metabolic syndrome due to short stature and high BMI.

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DISCLOSURE
The authors declare no conflict of interest.

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