Clinical Case Report

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Analysis of endocrine hormone metabolism level in a Chinese patient with mucopolysaccharidosis IVA

A case report

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Abstract

Rationale: Mucopolysaccharidosis IVA (Morquio A) is a catabolic mucopolysaccharide disorder caused by galactose-6-sulfate sulfatase deficiency. It is an autosomal recessive inherited disease. Previous reports on clinical characteristics of Morquio A mainly focused on growth retardation, skeletal deformities, and organ damage in children and adolescents, while the effects of mucopolysaccharide metabolism disorders on endocrine hormone metabolism level have not been reported. Herein, we reported the endocrine hormone metabolism in a case diagnosed as Morquio A.

Patient concerns: The patient was a 17-year-old girl with growth retardation, hearing loss, and severe skeletal dysplasia(scoliosis and chicken breast), and was evaluated to have normal nervous system function and intelligence by physicians.

Diagnoses: She was diagnosed as Morquio A based on gene analysis, mucopolysaccharide-related enzymes and her clinical features.

Interventions: The patient didn't accepted the enzyme replacement therapy.

Outcomes: She had a homozygous mutation of the GALNS gene. The b-glucuronidase content in the blood was reduced. The serum sodium, serum adrenocorticotropic hormone, and cortisol rhythms (8 AM) were decreased. The levels of PRA(plasma renin activity) , PAII(plasma angiotensin II), and PALD(plasma aldosterone) were elevated. Bone mineral density suggests osteoporosis. There were no abnormalities in bone metabolism indicators, growth hormone, thyroid hormone, and sex hormones. In summary, the level of endocrine hormones in patients with mucopolysaccharidosis IV changes.

Lessons: This is the report on endocrine hormone level in a patient with mucopolysaccharidosis IV in China. Due to the disease may have relatively incomplete adrenal function, which provides a basis for future understanding and diagnosis of this disease.

Abbreviations: ACTH = adrenocorticotropic hormone, GAG = glycosaminoglycan, KS = Keratan sulfate, Morquio A =mucopolysaccharidosis type IVA, MPS IVA = mucopolysaccharidosis type IVA. PRA = plasma renin activity, PAII = plasma angiotensin II, PALD = plasma aldosterone, SDS = Standard Deviation Score.

Keywords: galactose-6-sulfate sulfatase, GALNS, hormone level, mucopolysaccharidosis IVA

1. Introduction

Mucopolysaccharide is also called glycosaminoglycan (GAG). Mucopolysaccharidosis is a type of congenital disorder of mucopolysaccharide metabolism. It is an autosomal recessive inherited disease that is caused by loss of activity or functional defects of N- acetylgalactosamine-6-sulfatase.[1] Based on the clinical symptoms and lack of types of enzymes, mucopolysaccharidosis can be classified into 9 types. Of these, mucopolysaccharidosis IV is also known as Morquio syndrome, and can be divided into subtypes A and B, which are due to deficiencies of galactose-6-sulfate sulfatase and β-galactosidase, respectively.[2] The former is a GALNS mutation and the latter is a GLB1 mutation.[3] Previous studies on clinical characteristics of mucopolysaccharidosis IVA (Morquio A) were mainly focused on growth retardation, organ injury, and skeletal deformities.[4,5] However, the correlation between mucopolysaccharide metabolism disorders and endocrine system has not been reported. Endocrine diseases such as deficiencies of thyroid hormones and growth hormones can also result in growth retardation, bone metabolism abnormalities, mental development abnormalities, and abnormal levels of other endocrine hormones. These common features lead to misdiagnosis. Herein, we reported a case of Morquio IVA and analyzed the endocrine hormone level in the case, in order to further explore the changes of endocrine system in Morquio A disease and provide clues for understanding the disease.

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The patient signed the informed consent document.

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2. Subjects

The study was subject to approval by the ethics committee of Shanxi Medical University and informed consent was obtained from the guardian and the patient for the publication and accompanying images.

3. Case presentation

The patient was a 17-year-old girl. The patient's growth slowed 15 years ago, and her height and weight were significantly less than those of the same age. Her height and weight were less than the third percentile as compared to normal healthy children of the same gender, with precordial bulge and short limbs. However, these symptoms were undervalued and she was not treated. Eight years ago, she underwent laboratory examination, wherein anteroposterior and lateral films of thoracolumbar vertebrae and dual wrist joints revealed undifferentiated mucopolysaccharidosis. Five years ago, she started suffering from hearing loss (details unknown).

Since the onset of the disease, the patient had normal spirit, appetite, sleep, and regular menstruation with normal volume. Her last menstrual cycle was on December 3, 2015. She was unmarried, her parents and brother had normal height and weight. Her parents had consanguineous marriage, without family histories of special diseases. Physical examination of the patient revealed: height 102 cm, weight 19 kg, body mass index 18.3 kg/m^2, head circumference 53 cm, T: 37.2, P: 132 beats/min, blood pressure: 118/88 mm Hg, clear mind, poor spirit, normal intelligence, dark skin, pigmentation in face and lips, poor development of enamel, hirsutism, short neck, chicken breast, normal mammary development, inversion of nipples, clear breathing sound in both lungs, without dry rales, no pathological heart sounds and noise in auscultatory valve areas, soft abdomen without tenderness and rebound tenderness, normal bowel sound, kyphotic deformity, normal muscle tension in limbs, skeletal deformity, cubitus Valgus, short fourth toe in right foot, joint relaxation in both hands, hyperextension of wrists, without positive signs in nervous system symptoms, pigmentation, and hair in vulva.

4. Laboratory examination

1. Routine examinations
   No abnormalities were found in blood cell analysis, coagulation sequence, blood sedimentation, liver and renal functions, blood lipid, and stool routine: urinary ketone bodies (2+), venous fasting blood glucose 4.07 mmol/L (reference range: 3.9–6.0 mmol/24 h L), fasting insulin 10.31 mIU/L (reference range: 5–25 mIU/L), and blood uric acid 365 μmol/L (reference range: 150–350 μmol/L).
2. Electrolyte levels (Table 1)
3. Determination of endocrine hormones, bone metabolic indexes, and mucopolysaccharide-related enzymes (Tables 2–7)
4. Growth hormone excitation test (Table 8)
5. Family pedigree (Fig. 1)
6. Gene sequencing results (Fig. 2)

Table 1

Detection of hematuria electrolytes.

Electrolyte	Serum, mmol/L		Reference range, mmol/L	24-Hour urine, mmol/24 h	Reference range, mmol/24 h
K	4.30	4.67	3.5–5.3	8	51–100
Na	129	136	137–147	12	130–260
Cl	100	100	99–110	16	110–250
Ca	2.32	2.52	2.11–2.52	3.4	2.5–7.5
P		0.98	0.85–1.51	3.5	3.55
Mg		0.88	0.75–1.02	1.37	
Total urine, mL				450	

Table 2

Determination of serum ACTH, 24-hour urine free cortisol, and 24-hour 17-ketosteroids.

Glucocorticoid level	Serum ACTH, pmol/L	Cortisol rhythm, nmol/L			24-Hour urine free cortisol, nmol/L	24-Hour 17-ketosteroids, mg/24 h
		8 AM	4 PM	0 AM		
Before treatment	0.26 (1.10–13.2)	146.7 (171–536)	323.4 (64–327)	256.8	97.5 (100–379)	
After treatment	2.76 (1.10–13.2)	376.7 (100–379)			154.98 (100–379)	9.6 (6–14)

The patient suffered from nausea and vomiting at admission. After ACTH, cortisol rhythm, and 24-hour urine free cortisol testing, she was given sugar–salt–water for 2 days. A review of ACTH, 8 AM cortisol and 24-hour urine free cortisol was conducted after her symptoms had improved.
ACTH = adrenocorticotropic hormone.

Table 3

Determination of thyroid hormones.

Thyroid hormone	FT3, pmol/L	FT4, pmol/L	TSH, μIU/mL	A-TG, IU/mL	A-TPO, IU/mL
Result	4.91	20.78	0.950	509.2	182.5
Reference range	3.1–6.8	10–23	0.27–4.2	0–115	0–34

A-TG = antithyroglobulin antibodies, A-TPO = antithyroid peroxidase antibody, FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid-stimulating hormone.

Table 4

Determination of sex hormones.

Sex hormone (luteal phase)	E2, pmol/L	FSH, mIU/mL	PROG, nmol/L	LH, mIU/mL	TEST, nmol/L	PRL, μIU/mL
Result	765.4	1.75	23.96	0.474	1.32	343
Reference range	161–774	1.7–7.7	5.3–86	1.0–11.4	0.1–1.67	102–496

E2 = estradiol, FSH = follicle stimulating hormone, LH = luteinizing hormone, PRL = prolactin, PROG = progesterone, TEST = testosterone.

Table 5

Determination of RAAS.

RAAS (supine position)	PRA, ng/mL per h	PAII, pg/mL	PALD, pg/mL
Result	11.15	157.65	275.19
Reference range	0.05–0.79	28.2–52.2	59–174

PAII = plasma angiotensin II, PALD = plasma aldosterone, PRA = plasma renin activity, RAAS = renin–angiotensin–aldosterone system.

Table 6

Determination of bone metabolic indexes.

Bone metabolic indexes	Osteocalcin, ng/mL	PINP, ng/mL	25-(OH)VD, nmol/L
Result	28.5	43.74	44.14
Reference range	13–48	15.13–58.59	≥75

P1NP = procollagen type 1 N-terminal propeptide.

Table 7

Determination of mucopolysaccharide-related enzymes.

Seroenzyme test	IDUA, nmol/1 h per mg	β-Gal, nmol/1 h per mg	β- Glucuronidase, nmol/1 h per mg	Acetyl-CoA: α-acetylglucosaminyltransferase activity, nmol/17 h per mg	α-N-NAG, nmol/17 h per mg
Result	25.93	148.16	116.66	15.70	19.58
Reference range	>21	>90	>146	>8.6	>16

α-N-NAG = α-N-acetylglucosaminidase, β-Gal = β-galactosidase, IDUA = α-L-iduronidase.

Table 8

IGF-1 level and growth hormone challenge test.

	IGF-1, ng/mL	GH, ng/mL	GH 30 minutes, ng/mL	GH 60 minutes, ng/mL	GH 90 minutes, ng/mL
Result	244	3.45	17.63	7.53	3.18
Reference range	193–731	<5	<5	<5	<5

The growth hormone challenge test was performed by arginine challenge. A 5% to 10% solution of 0.5 g/kg (≤30 g) arginine was prepared with water and intravenously injected for 30 minutes. The blood samples were collected at 0, 30, 60, and 90 minutes.
GH = growth hormone, IGF-1 = insulin-like growth factor 1.

7. Chromosome examination: 46,XX
8. Auxiliary examination

Changes in X-rays of chest, hands, and lower extremities (Fig. 3): Both lungs appeared blurred and disordered, the hilar structure was unclear, and cardiodiaphragm did not show abnormalities. The thoracolumbar vertebrae were flat, the anteroposterior diameter was increased, the superior and inferior vertebrae were irregular, the anterior edge was rounded with centralized tongue-like protrusion, the L1 and T12 vertebrae were wedged, receded, the anterior edges were centrally pungent, and all thoracolumbar vertebrae were receded. The distal ends of bilateral ulna and radius were irregular, with absence of metacarpal bone shortening. The knee joint spaces were widened, the intercondylar eminences were flat, the articular surfaces were rough, the inner plateau of the left tibia was irregular, bone fragments were locally visible, bone trabecular was invisible, and the bone end was deformed. The ankle joint spaces were widened, the bone ends were irregular with bone fragments, the ankle bones were deformed, and hardening was visible. The proximal toes were irregular.

5. Discussion

Mucopolysaccharide is also known as GAG. Mucopolysaccharidosis is a rare genetic disease characterized by GAG catabolic abnormalities, which tends to influence the cell signaling pathway, sequestration chelation of the extracellular humoral factors as well as the interaction between cells, and eventually leads to functional and structural disorders of multiple organs.[4] Growth retardation and skeletal deformities are the most

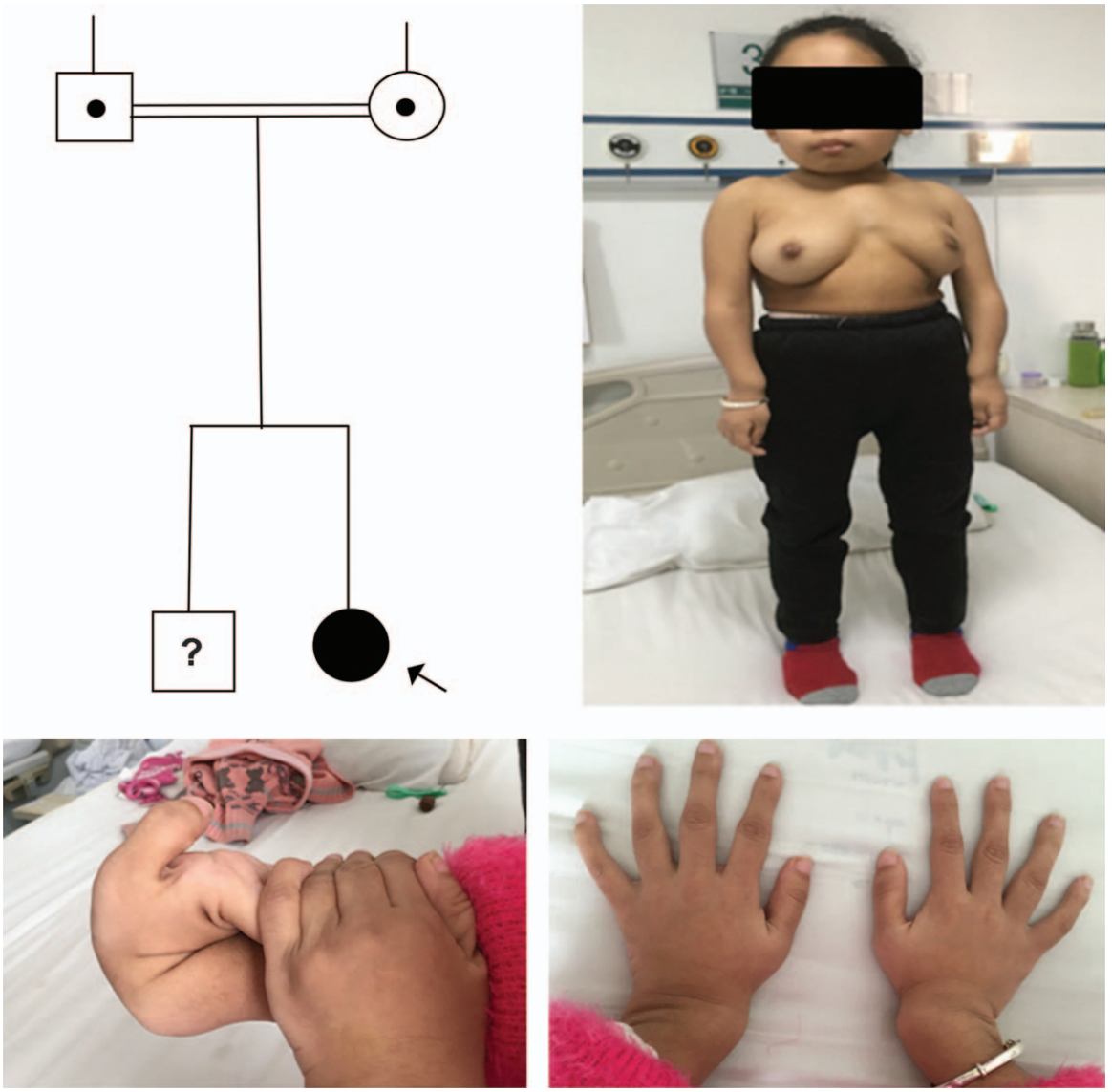

Figure 1. Family pedigree: Two generations were examined in this report. A dark arrow indicates the proband. Squares indicate male members. Circles indicate female members. Symbol with a question mark in the center represents the family member who was not examined in this report. Symbol with black color represent the daughter confirmed with disease. Symbols with a dot in the center represent family members who only carry the mutation.

common clinical manifestations of the disease. The visual system, auditory system, cardiovascular system, and respiratory system can also be affected.[5] The patient in this report showed growth retardation since she was 2 years old. Her height at admission was only 102 cm when she was 17 years old, which was −2 SD lower than the average height of the peers, with normal intelligence. The special features of the patient included short neck, prominent jaw, poor development of enamel, skeletal deformity, ligament relaxation, and excessive motor of joints. All the clinical symptoms were consistent with manifestations of mucopolysaccharidosis. Seroenzyme activity determination was considered the gold diagnostic criteria for this case, while gene sequencing was used to further clarify the gene mutation locus. The results showed a decrease in seroenzyme level and c.502_503 del GG ins TT (p.Gly168Leu) mutation. Parents of patients with mucopolysaccharidosis type IVa (MPSIVA), caused by mutations in the GALNS gene, often carry disease-causing mutations. Parents carrying disease-causing mutations each carry a 25% risk of having children who may be patients. Other relatives of the patients' parents are also at risk of carrying the same pathogenic mutation. The mutation was a mini deletion insertion mutation (changing the amino acid at position 168 of the encoded protein from Gly to Leu) without causing frameshift. This mutation was detected in MPSIVA patients and p.Gly168Arg was also detected in MPSIVA patients.[6,7] Based on the clinical symptoms, seroenzyme level, imaging examination and gene sequencing, the patient was diagnosed as mucopolysaccharidosis IVA. The parents of the patient had consanguineous marriage, without clinical phenotype, and their gene sequencing showed heterozygous mutation. Their son was 173 cm tall, gene sequencing was not performed, while their daughter suffered from the disease. These were consistent with the hidden genetic rule. In addition, the mutated gene locus could be determined using gene sequencing.

The effects of mucopolysaccharide metabolic abnormalities on the endocrine system have not been reported. In addition to

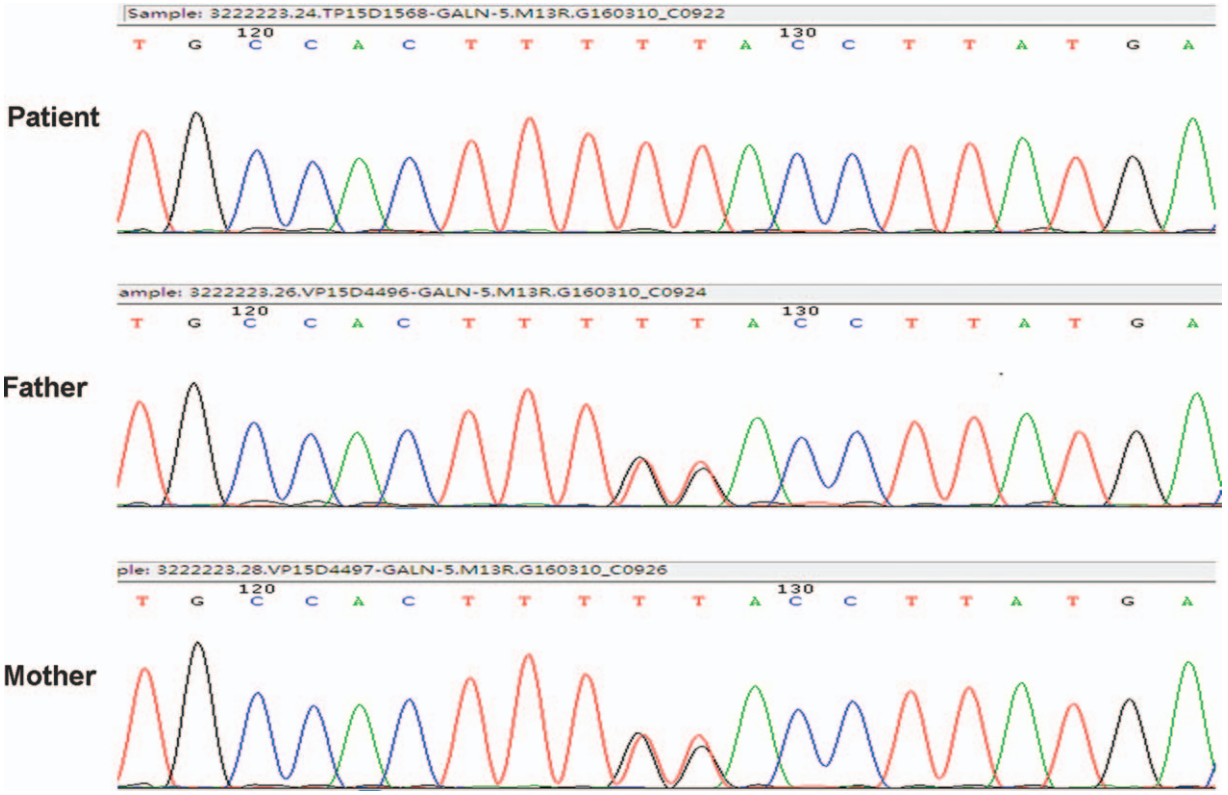

Figure 2. Polymerase chain reaction-sequencing of the GALNS gene in the patient with Morquio IVA disease. The parents of the patient were carriers for the mutations. The patient had homozygous mutation for the c.502_503 del GG ins TT (p.Gly168Leu). The brother was not examined in this report.

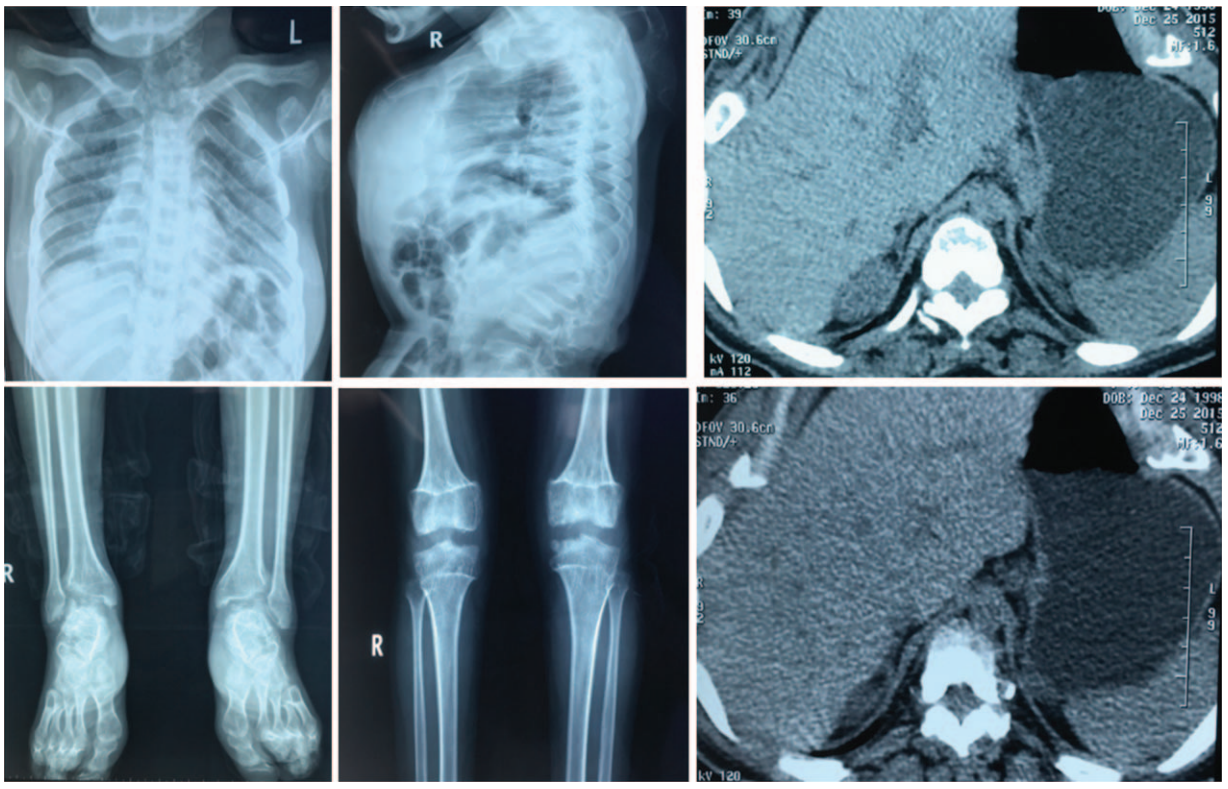

Figure 3. Changes in X-ray of the patient with mucopolysaccharidosis. Bilateral adrenal squeeze. No abnormalities were found in electrocardiogram, abdominal color Doppler ultrasound, and pituitary magnetic resonance imaging plain scan. Ultrasonic cardiogram: Pulmonary artery was widened, the tricuspid showed mild regurgitation, and the pulmonary artery pressure was in the normal range. Bone density examination showed osteoporosis. Lumbar vertebrae T scale: −4.0, Z scale: −4.8; left hip T scale: −3.1, Z scale: −3.4.

growth retardation, skeletal dysplasia, and hearing loss, the patient in this report also suffered from abnormalities of some endocrine functions. At admission, she had nausea and vomiting, urine ketone positive, a low serum sodium level after improvement, a low serum adrenocorticotropic hormone (ACTH) level, and disappearance of cortisol rhythm. After receiving symptomatic rehydration, the patient's symptoms improved. The review showed that the serum ACTH level was still low, and there were no abnormalities in pituitary magnetic resonance imaging and adrenal computed tomography, which suggests that the patient may suffer from hypothalamic–pituitary–adrenal axis dysfunction, and is unable to meet the body's demand for glucocorticoids in the stress state. However, we were unable to further evaluate the function because the patient refused to undergo adrenocorticotropic hormone-releasing hormone stimulation test. We speculate that a cortical hypofunction in the stress state may be associated with inhibition of visceral function due to compression caused by skeletal deformities. Furthermore, studies have found that β-glucuronidase plays a physiological role in the metabolism of steroid hormones.[8,9] Thus, a low level of glucocorticoid in the patient with stress may be associated with β-glucuronidase deficiency. Meanwhile, the patient showed high levels of renin–angiotensin–aldosterone, which may be associated with a low level of serum sodium and insufficient circulating blood volume due to nausea and vomiting at admission.

Mucopolysaccharidosis IV refers to sulfuric acid metabolic disorders. Bone and cartilage are the major tissues for the synthesis of sulfuric acid, which are involved in tissue remodeling and cartilage destruction and/or repair during growth. In mucopolysaccharidosis type IVA (MPS IVA) patients, a large amount of keratan sulfate (KS) is released to destruct cartilage tissue before closure of epiphysis, but KS in cartilage tissue is significantly decreased and KS level in blood is increased after closure of epiphysis. An increased KS level in the blood of MPS IVA patients is associated with cartilage catabolic rate. As shown in Fig. 1, the patient's skeleton was excessively stretched, and the skeletal tissue was osteoporotic, which was associated with KS metabolic disorders.[10,11] The patient had normal levels of thyroid hormones and sex hormones. Some studies have reported that male or female patients with mucopolysaccharidosis IVA are fertile, but their risk of giving birth is higher than the general population and the offsprings may inherit the disease. Therefore, they should undergo evaluation by multidisciplinary doctors and nurses before pregnancy and after delivery, in order to reduce the risk to fetal growth and development.[12]

Montano et al conducted a longitudinal and cross-sectional study of 354 Morquio A patients using questionnaires, and found that the average length/height of infants and young children with Morquio A was similar to that of general population, but it was lower than the normal range (<−2 Standard Deviation Score) when they were about 4 years old, and the growth rate was also decreased.[13] Polgreen and Miller reported 2 cases (13- and 17-year-old girls, respectively) with Morquio A, and found that their growth hormone levels were in the normal range after the stimulation test,[14] which was similar to our findings. The difference was that the level of IGF-1 was normal in our patient, but was lower in the cases reported by Polgreen and Miller, which suggests that the growth retardation in these patients is not caused by insufficient growth hormone secretion.

In addition to skeletal deformities, growth retardation, and hearing loss, the patient in this report also suffered from abnormal hormone levels of some endocrine systems, which mainly manifested as abnormalities of glucocorticoid and mineralocorticoid. The potential reasons could be as follows: multiple organs of the patient are compressed due to her special physique; the effects of deficiency or abnormal activity of mucopolysaccharide enzyme on the endocrine hormones, which requires further studies.

The limitations of this study include: only 1 case was reported. Adrenal function was not evaluated because the patient refused to undergo adrenocorticotropic hormone-releasing hormone stimulation test. Gene sequencing of the patient's brother was not performed.

Author contributions

Investigation: Linxin Xu, Yi Ren, Jianhong Yin, Jing Yang, Yunfeng Liu, Jin Zhang, Yi Zhang, Chenyu Xiang, Luyang Yang.
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Visualization: Linxin Xu.
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Writing – review & editing: Linxin Xu, Yi Ren, Jianhong Yin, Jing Yang, Yunfeng Liu, Jin Zhang, Yi Zhang, Chenyu Xiang, Luyang Yang.

References

[1] Tomatsu S, Fujii T, Fukushi M, et al. Newborn screening and diagnosis of mucopolysaccharidoses. Mol Genet Metab 2013;110:42–53.
[2] Stevenson DA, Rudser K, Kunin-Batson A, et al. Biomarkers of bone remodeling in children with mucopolysaccharidosis types I, II, and VI. J Pediatr Rehabil Med 2014;7:159–65.
[3] Wood TC, Harvey K, Beck M, et al. Diagnosing mucopolysaccharidosis IVA. J Inherit Metab Dis 2013;36:293–307.
[4] Hamza A, Khawar S, Ibrahim A, et al. A second reported malignancy in a patient with Morquio syndrome. Autops Case Rep 2017;7:9–14.
[5] Hendriksz CJ, Harmatz P, Beck M, et al. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. Mol Genet Metab 2013;110:54–64.
[6] Wang Z, Zhang W, Wang Y, et al. Mucopolysaccharidosis IVA mutations in Chinese patients: 16 novel mutations. J Hum Genet 2010;55:534–40.
[7] Bunge S, Kleijer WJ, Tylki-Szymanska A, et al. Identification of 31 novel mutations in the N-acetylgalactosamine-6-sulfatase gene reveals excessive allelic heterogeneity among patients with Morquio A syndrome. Hum Mutat 1997;10:223–32.
[8] Tohyama O, Imura A, Iwano A, et al. Klotho is a novel beta-glucuronidase capable of hydrolyzing steroid beta-glucuronides. J Biol Chem 2004;279:9777–84.
[9] Shibasaki H, Tanabe C, Furuta T, et al. Hydrolysis of conjugated steroids by the combined use of beta-glucuronidase preparations from helix pomatia and ampullaria: determination of urinary cortisol and its metabolites. Steroids 2001;66:795–801.
[10] Khan S, Almeciga-Diaz CJ, Sawamoto K, et al. Mucopolysaccharidosis IVA and glycosaminoglycans. Mol Genet Metab 2017;120:78–95.
[11] Dung VC, Tomatsu S, Montano AM, et al. Mucopolysaccharidosis IVA: correlation between genotype, phenotype and keratan sulfate levels. Mol Genet Metab 2013;110:129–38.
[12] Stewart FJ, Bentley A, Burton BK, et al. Pregnancy in patients with mucopolysaccharidosis: a case series. Mol Genet Metab Rep 2016;8:111–5.
[13] Montano AM, Tomatsu S, Brusius A, et al. Growth charts for patients affected with Morquio A disease. Am J Med Genet A 2008;146A:1286–95.
[14] Polgreen LE, Miller BS. Growth patterns and the use of growth hormone in the mucopolysaccharidoses. J Pediatr Rehabil Med 2010;3:25–38.