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Management of scoliosis in a pediatric patient with lysyl hydroxylase-3 deficiency: a case report

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Abstract

Background A rare case report of lysyl hydroxylases deficiency undergoing scoliosis surgery.

Case presentation An 8-year-old Persian patient with a known case of lysyl hydroxylases deficiency presented with scoliosis. On physical examination, he had course facial hair, elbow flexion contracture, and knee flexion contracture. He had a history of eye surgery, clubfoot, and hearing problems. He underwent scoliosis surgery with growing rod instrumentation.

Conclusion Surgery can be done in these patients with caution, and the surgeon and anesthesiologist should be aware of potential complications during and after surgery.

Keywords Lysyl hydroxylase-3 deficiency, Case report, Scoliosis

Introduction

Lysyl hydroxylases (LH) are catalysts of collagen lysines through hydroxylation and their subsequent glycosylation and play an essential role in forming the extracellular matrix [1]. There are three LH enzyme isoforms: LH1, LH2a/b, and LH3. These enzymes act in concert with prolyl hydroxylases in the endoplasmic reticulum [1]. LH enzymes are also found as proteins resident in the endoplasmic retinaculum. LH3 [encoded by procollagen lysine, 2-oxoglutarate-5-dioxygenase 3 (POD3)] is presented in the extracellular space and can interfere with cellular secretion mechanisms [1]. Any PLOD genes encoding LH mutations are associated with connective tissue disorders such as Ehlers–Danlos syndrome [1, 2]. Altered collagen glycosylation, secretion, and basement membrane formation are the results of PLOD3 gene mutations [1].

LH3 deficiency is a rare connective tissue disorder characterized by congenital malformations that severely affect many tissues and organs [2]. The prevalence of LH3 deficiency is less than one per million population [3]. Skeletal abnormalities, such as progressive scoliosis, osteopenia, clubfoot, and pathologic fractures, may occur. Other manifestations of this disease have been reported to include ocular involvement (flat retina, myopia, and cataracts) and hair, nail, and skin abnormalities (coarse, abnormally distributed hair, skin blistering, reduced palmar folds, and hypoplastic nails). Patients also present with intrauterine growth retardation, facial dysmorphism (flat facial profile, low set ears, shallow orbits, short and upturned nose, and down-turned corners of the mouth), and joint flexion contractures. Other

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reported features are growth and developmental retardation, bilateral sensorineural deafness, friable diaphragm, and later onset of spontaneous vascular rupture. As this is a rare occurrence, the diagnosis is confirmed by whole-exome sequencing, and the prognosis has yet to be defined. Here, we describe a case of a young man who underwent spinal surgery due to progressive scoliosis.

The case

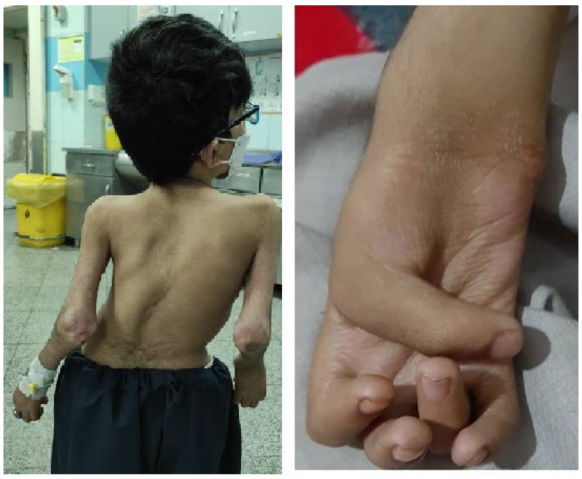
An 8-year-old American Society of Anesthesiologists (ASA) II, Persian patient presented to the orthopedic department with severe scoliosis. He was previously diagnosed with a case of LH3 deficiency. The diagnosis of lysyl hydroxylase deficiency was made in 2019 based on clinical symptoms and genetic studies at the Department of Dermatology and Cutaneous Biology at Thomas Jefferson University Hospital. We used the CARE reporting guidelines for this case [4].

On physical examination, the body temperature of the patient was 36.5 °C, the heart rate (HR) 80 beats/minute, the respiratory rate (RR) 19 breaths/minute, and the noninvasive blood pressure (NIBP) 100/65 mmHg. At preoperative airway assessment, the Mallampati classification was class I, and neck mobility was normal. The dentition appeared to be normal. The jugular vein size and heart sounds were normal. No abnormality was noted in the thorax other than severe scoliosis, and nothing notable was noted during the physical examination of the abdomen. He had several facial deformities, such as anteverted nostrils, down-turned corners of the mouth, and an elongated philtrum. He was also deaf in his left ear, with reduced hearing in his right ear. The patient had an auricle anomaly and low-set ears. He had shallow orbits, the right eye had ptosis and blindness, and the left eye had decreased vision and myopia. The patient had a history of eye surgery to treat congenital glaucoma as well as ptosis. He had coarse hair and nail dysplasia. Examination of the upper extremities revealed elbow flexion contracture and thenar muscle atrophy (Fig. 1). In infancy, the patient underwent a plaster cast to treat clubfoot. He had a flexion deformity in both knees due to a combination of bony, capsular, and ligament deformity.

He had no history of other illnesses and was not receiving any specific medication. Also, there was no family history of hereditary diseases.

In the studies, the patient's chest X-ray was normal, except for scoliosis and severe diaphragmatic eventration (Fig. 2). Electrocardiography was normal. Transthoracic echocardiography showed mild tricuspid regurgitation without pulmonary hypertension.

The patient had a history of mild intracranial hemorrhage 3 years ago. Therefore, a computed tomography (CT) scan of the brain was performed, observing bilateral calcification of the globus pallidus and subcortical calcification and thickening of the associated cortex in the left parietal lobe. The left Sylvian fissure widening was also reported. The patients' laboratory tests were also within normal limits. He did not cooperate with spirometry. Due to progressive scoliosis and a previous history of pneumonia, the decision to undergo corrective scoliosis surgery was made.



(A) (B)

Fig. 1 (**A**) Posterior view from the patient. (**B**) Right hand

In the operating room, the body temperature of the patient was 36.5 °C, the HR was 90 beats/minute, the RR was 20 breaths/minute, the blood pressure was 105/70 mmHg, and the oxygen saturation was 97% (which increased to 99% after increasing FiO_2 by 80% via face mask). He was premedicated by intravenous (IV) midazolam 1 mg and IV fentanyl 50 µg via a previously inserted IV catheter G20. ECG, NIBP, and pulse oximetry were attached to monitor his vital signs. Induction of anesthesia was performed by IV propofol 50 mg and 15 mg atracurium, as there were no signs of difficulty in airway management. After successful intubation by spiral ETT number 5.5 (grade 1 Cormack–Lehane classification), capnography was used as respiratory monitoring, but due to flexion deformity of both hands, it was not possible to establish an arterial line for invasive blood pressure monitoring. As somatosensory evoked potential (SSEP) and motor evoked potential (MEP) were planned to be used intraoperatively, muscle relaxant was not repeated during the operation. Maintenance of anesthesia was established with propofol 100–200 µg/kg/hour and remifentanil 10 µg/hour via and IV catheter G18. To monitor anesthesia depth, a bispectral index monitor, BIS VISTA (Aspect Medical Systems, Newton, MA) was used and maintained within the range of 40–60. Afterward,

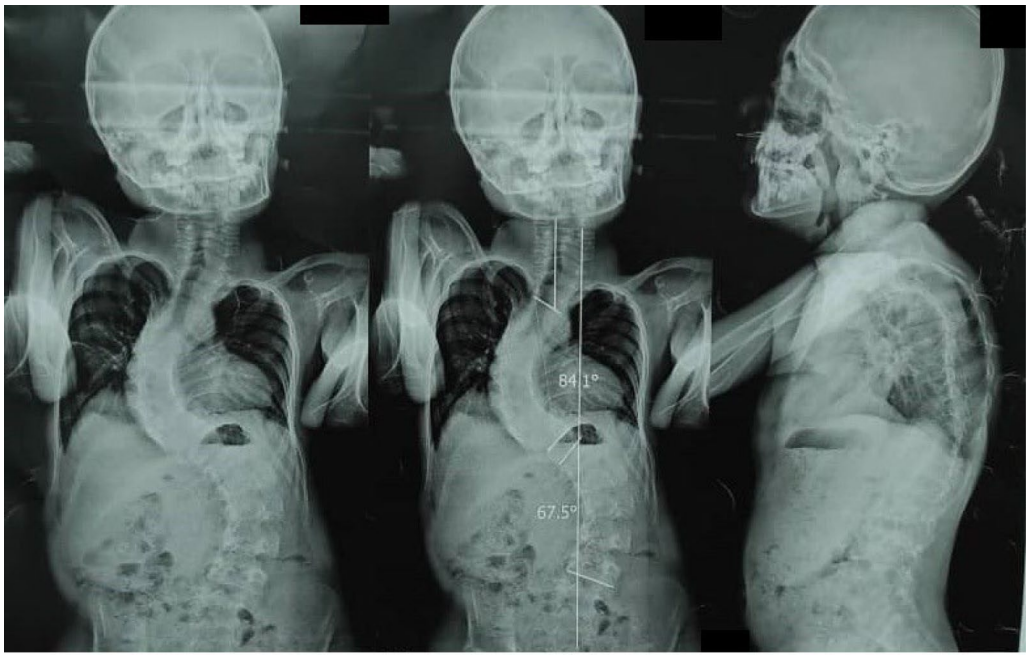


Fig. 2 Preoperative radiograph

the position was changed to prone without any significant hemodynamic change. He had two structural curves, an 84.1° thoracic curve and a 67.5° lumbar curve (Cobbs method). The upper instrumentation (pedicle screws) of T2 and T3 and the lower instrumentation of L3 and L5 were planned through the mid-posterior incision. The paravertebral muscles were not elevated except during pedicle screw insertion. The pedicle screws were connected by the growth rods, which could be lengthened every 6–9 months. Due to the growth condition of this patient, the fusion technique was not chosen (Fig. 3). During the operation, the hemodynamics were stable, and the blood pressure was maintained between 110/70 and 130/80. The intraoperative period was uneventful, with blood loss of almost 150–200 mL. The fluid replacement was with 500 mL of normal saline followed by 500 mL of Ringer's solution. The anesthetics were gradually discontinued, and the tracheal tube was extubated upon awakening. Total operating time was 160 minutes, and anesthesia time was 180 min. He was transferred to the intensive care unit and discharged 5 days later after rehabilitation without any morbidity.

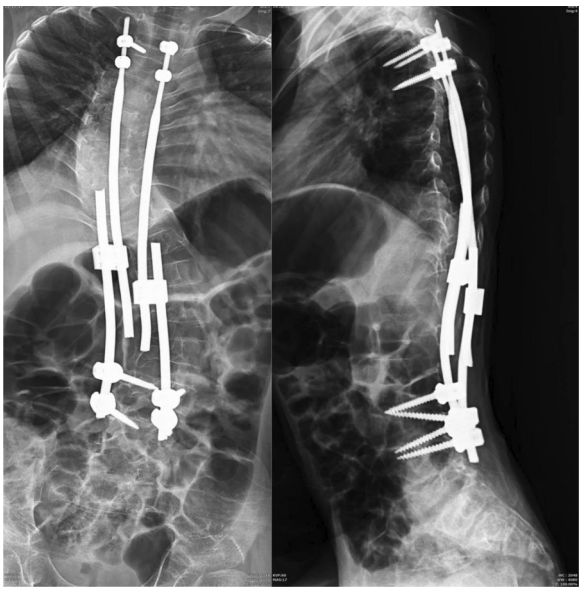


Fig. 3 Postoperative radiographs

Discussion

Lysyl hydroxylase-3 deficiency, also known as bone fragility contractures arterial rupture deafness syndrome, is a rare autosomal recessive connective tissue disorder. It is characterized by multiple tissue and organ involvement, including skeletal abnormalities; ocular involvement and hair, nail, and skin abnormalities; intrauterine growth retardation; facial dysmorphism; and joint flexion contractures [2, 3, 5]. Growth and development retardation, bilateral sensorineural deafness, friable diaphragm, and late-onset spontaneous vascular rupture have also been reported [2, 6]. The disease is caused by a mutation in the PLOD3 gene at

Table 1 Anesthetic considerations in LH3 deficiency

Anesthetic considerations	Etiology
Difficult intubation	Facial deformity
Restrictive lung disease	Scoliosis
Difficult cooperation	Deafness and mental retardation
Positioning	Skin blister, easy bruising, vascular rupture
Intravenous and intra-arterial access	Vascular rupture

position 7q22.1, which codes for lysyl hydroxylase-3, which leads to the biosynthesis of highly glycosylated type IV and VI collagen in animals [3, 7, 8].

This was first reported by Salo *et al.*, who described a woman with connective tissue disorder secondary to LH3 deficiency with intrauterine growth retardation and craniofacial features such as a flat facial profile, low set ears, shallow orbit, short upturned nose, and down-turned corners of the mouth. She also had skeletal abnormalities, including talipes equinovarus, progressive scoliosis, osteopenia, and pathologic fractures. She had platyspondyly, small femoral epiphyses, a J-shaped sella turcica, and a small odontoid. Other manifestations were severe bilateral sensorineural deafness, myopia, and cataracts. Skeletal muscle mass was reported as poor, but no studies of muscle function were performed. Her skin was blistered and bruised easily. In the second decade, she had a spontaneous cerebral arterial hemorrhage associated with hemiplegia and also a rupture of the popliteal aneurysm. When she was 14 years old, a subsequent CT scan showed severe dilatation of both internal carotid arteries. Her social skills and development were also delayed [2, 5, 7].

Our patient had almost all the characteristics of the above case. He had similar craniofacial features such as shallow orbits, a flat facial profile, low-set ears, and upturned and down-turned corners of the mouth, but he did not have a short nose, unlike the the aforementioned patient. Skeletal abnormalities were similar (progressive scoliosis and platyspondyly, talipes equinovarus, osteopenia, and pathologic fracture). He had deafness in the left ear, reduced hearing in the right ear, and myopia but not cataracts, as in the aforementioned care. Also, unlike the patient reported by Salo, the patient had glaucoma and despite the surgery, he eventually lost sight in his right eye. The patient's left eye was also affected. He had no history of skin blisters or easy bruising. As mentioned above, 3 years ago, he had suspected mild intracranial hemorrhage with no residual deficits. This is in contrast to what has been reported for proband.

Due to time constraints and lack of legal consent, it was not possible to examine the cerebral arteries and the condition of the sella turcica. Also due to similar restrictions, we cannot fully evaluate the patient for global developmental delay, fetal growth restriction, and postnatal growth retardation. However, it is clear that due to the height, weight, and size of the head circumference, these sizes are less than normal values for his age. Despite the patient's calmness and quietness, he cooperated in examining and answering questions with a few words.

In our patient, endotracheal intubation went smoothly, and hemodynamics were stable after anesthesia induction and tracheal intubation. Because of the risk of spontaneous vascular rupture, it makes sense to avoid forced or prolonged endotracheal intubation. A similar problem can exist with invasive monitoring using the arterial line. However, we could not establish arterial access. It should be noted that scoliosis itself can also complicate the anesthetic process. Five days after the operation, the patient was discharged from the hospital in good general condition. The patient's family was advised to refer him to the orthopedic department for further evaluation.

There are some similarities between these two cases and Stickler syndrome [2] such as a flat facial profile, myopia, and deafness. However, there is no osteopenia, joint problems, growth abnormalities, nail and skin problems, or spontaneous vascular ruptures in Stickler syndrome. There are also similarities to Ehlers–Danlos syndrome type IV in terms of spontaneous arterial rupture and osteopenia; although, progressive scoliosis and head and face characteristics are not seen in this syndrome [2].

Due to the abnormality in collagen synthesis caused by LH3 deficiency, the main complications during and after surgery seem to be related to arterial rupture. Therefore, it is very important to pay special attention to the patient's position and to avoid drastic hemodynamic changes during anesthesia induction and surgery. It should also be noted that in patients with scoliosis, the aorta is prone to damage and rupture due to direct surgical injury. A case of pseudoaneurysm and rupture of the aorta in a patient with Ehlers–Danlos syndrome type IV after spinal surgery has been reported [6].

The main limitation of our study was the lack of access to details of the patient's genetic reports. In addition, the patient lives in a remote town, and it has been difficult to obtain further evaluations of the patient. To our knowledge, no other cases of this disease have been reported. Therefore, no further comparison was possible.

Conclusion

In summary, considering the etiology of LH3 deficiency, it is important to pay close attention to potential vascular damage during surgery. Although we did not encounter any issues during our surgery, it is crucial to be vigilant in

this regard. Working together with surgeons and intensive care physicians can help identify vascular damage much earlier and initiate appropriate therapies (Table 1).

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Declarations
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Author contributions
MA and AM conceived and designed the analysis, collected the data, contributed data, and wrote the paper, and were the surgeons responsible for the surgery. AT and DA conceived and designed the analysis, contributed data or analysis tools, performed the analysis, wrote the paper, and were the anesthesiologist responsible for the patient. MF and MB conceived and designed the analysis, collected the data, contributed data, and wrote the paper.

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Data availability
The data is available at the request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal (the consent is in the Persian language, but it can be translated to English, and the hospital can confirm this in a separate email)

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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