CLINICAL VIGNETTE

The Sequelae of Larsen Syndrome

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A 60-year-old female presented with bilateral hip pain 2 months after bilateral hip replacement. She had mild to moderate constant pain in the hips and thighs when she walked. Methocarbamol, meloxicam and oxycodone provided pain relief but she was eager to wean off of medications. She was working with physical therapy and was seeing gradual improvement in her hip range of motion. She was seeking another opinion for an underlying reason for her long history of joint problems.

Her past medical history revealed that she was of Ashkenazi Jewish descent. She was born with bilateral clubfeet. She had frequent dislocations of her hips and knees. In childhood, she had multiple surgeries to correct the clubfoot deformity and knee dislocations. She later had bilateral knee replacements, surgery for a femoral fracture and the recent bilateral hip replacements.

On physical exam, her vital signs were within normal limits. Height was 5 feet and 1 inch with a BMI of 34. She had mild frontal bossing and a flat nasal bridge. Both tympanic membranes and ear canals were normal in appearance with a right hearing aid present. Pupils were equal, round, and reactive to light, cardiac, regular rate and rhythm without murmurs. She had a depressed sternum with pectus excavatum, upper extremities with rhizomelia (disproportion of the length of the proximal limb) as well as hypomobility of the wrists and fingers. Spinal exam revealed scoliosis. She had spatulate thumbs. The lower extremities also showed rhizomelia. She had severe deformities of both feet with valgus deviaton and overlap of the 4^{th} and 5^{th} toes. Gait as wide based.

The bilateral hip joints were free of edema, erythema and warmth. Range of motion was mildly decreased for flexion, extension, abduction, adduction, internal rotation and external rotation bilaterally. Her surgical wounds from her recent bilateral hip surgery had healed.

Labs and Studies

X-rays of the bilateral hips and pelvis revealed that the hardware alignment and positioning were stable. There was a healed femoral fracture as well as a nonunited fracture of the left greater trochanter. A CT scan of the left hip showed some rotation of the hip components, with the right femoral neck anteverted at 19 degrees and the left femoral neck component retroverted at 13 degrees. Genetic testing was pursued to look for an underlying etiology for her joint dislocations. The testing revealed the FLNB mutation. This is a mutation in the filamin B protein that causes Larsen syndrome.

Treatment Course

Pool therapy, acupuncture, and trigger point injections helped with improving pain control. She had orthotics made for both clubfeet. Nortriptyline was added to her medication regimen and she was able to stop the methocarbamol. Her oxycodone use decreased and she was using tramadol and meloxicam with more limited oxycodone use for severe episodes of pain. She decided against further hip surgery after considering the risks and benefits despite the change in position of the femoral components.

Echocardiogram showed no septal defect, significant valvular disease or dilation of the aortic root. Repeat bone density testing showed continued improvement of osteopenia on denosumab.

Discussion

Larsen syndrome (LS) is an osteochondrodysplasia that leads to joint dislocations as well as craniofacial abnormalities.[1] It is caused by a mutation in the FLNB gene which encodes the filamin B protein.[1] Filamin B is an important cystoskeletal protein.[1] Common features of Larsen syndrome include foot deformities as well as hip, knee and elbow dislocations.[1] Spatula-shaped fingers, hypertelorism, a depressed nasal bridge, cleft-palate, scoliosis, kyphosis, and short stature are all common features.[1] Hearing loss can also occur due to skeletal deformities of the auditory ossicles.[2] Our patient was already utilizing a hearing aid and had many of the typical craniofacial abnormalities and skeletal deformities.

FLNB mutations can also lead to reduction in bone mineral density.[3] Our patient had a prior fragility fracture of the femur. In addition to its impact on bones, the FLNB mutations can also contribute to weakness and imbalance of the muscles.[3] Our patient had been diagnosed with myofascial pain syndrome and was seeing benefit with our East-West Medicine with acupuncture and trigger point injections.

Joint pain from dislocations and skeletal deformities often lead to surgical intervention for patients with LS. However, they are

at higher risk for perioperative complications. Cervical spine instability is common with special care when positioning for anesthesia.[4] Laryngo-tracheomalacia is also a feature of LS and can predispose the patient to respiratory compromise.[4] Cervical spine xrays prior to surgery as well as use of supraglottic airway devices when possible can help decrease these risks during surgery.[4]

Cardiac anomalies have also been observed in patients with LS including atrial septal defects, ventricular septal defects and patent ductus arteriosus.[5] These underlying abnormalities contribute to later onset of aortic root dilation, aortic insufficiency, mitral valve insufficiency, and aneurysm of the ductus arteriosis.[5] Monitoring with periodic echocardiograms can assist with identifying these cardiac changes.

Currently, surgical intervention, bracing, and orthotics are the mainstays of treatment for managing the skeletal deformities that develop with LS. Dealing with chronic pain can be an unfortunate reality for many patients with LS and a team approach is needed to maintain good quality of life. Gene therapy may hold promise for better treatment options in the future.

REFERENCES

1. **Bicknell LS, Farrington-Rock C, Shafeghati Y, Rump P, Alanay Y, Alembik Y, Al-Madani N, Firth H, Karimi-Nejad MH, Kim CA, Leask K, Maisenbacher M, Moran E, Pappas JG, Prontera P, de Ravel T, Fryns JP, Sweeney E, Fryer A, Unger S, Wilson LC, Lachman RS, Rimoin DL, Cohn DH, Krakow D, Robertson SP.** A molecular and clinical study of Larsen syndrome caused by mutations in FLNB. *J Med Genet.* 2007 Feb;44(2):89-98. Epub 2006 Jun 26. PubMed PMID: 16801345; PubMed Central PMCID:PMC2598053.
2. **Girisha KM, Bidchol AM, Graul-Neumann L, Gupta A, Hehr U, Lessel D, Nader S, Shah H, Wickert J, Kutsche K.** Phenotype and genotype in patients with Larsen syndrome: clinical homogeneity and allelic heterogeneity in seven patients. *BMC Med Genet.* 2016 Apr 6;17:27. doi: 10.1186/s12881-016-0290-6. PubMed PMID:27048506; PubMed Central PMCID: PMC4822278.
3. **Xu Q, Wu N, Cui L, Wu Z, Qiu G.** Filamin B: The next hotspot in skeletal research? *J Genet Genomics.* 2017 Jul 20;44(7):335-342. doi:10.1016/j.jgg.2017.04.007. Epub 2017 Jul 6. Review. PubMed PMID: 28739045.
4. **Rai A, Trikha A, Kumar A, Chandran R.** Supraglottic airway and caudal epidural for anesthetic management of a child with Larsen syndrome. *J Anaesthesiol Clin Pharmacol.* 2016 Apr-Jun;32(2):266-7. doi: 10.4103/0970-9185.173369. PubMed PMID: 27275063; PubMed Central PMCID: PMC4874088.
5. **Liang CD, Hang CL.** Elongation of the aorta and multiple cardiovascular abnormalities associated with larsen syndrome. *Pediatr Cardiol.* 2001 May-Jun;22(3):245-6. Pub Med PMID: 11343154.

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