CLINICAL VIGNETTE

Pediatric Autosomal Dominant Osteoporosis

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Case Presentation

An 18-year-old male with no significant past medical or surgical history presents with right hip pain after a low-energy fall. An X-ray shows an acute subcapital to cervical fracture of the right femoral neck and he is referred to orthopedics for closed reduction and percutaneous pinning. Due to the fragility fracture and high level of suspicion for osteoporosis, he is also referred to endocrinology.

Examination reveals a BMI of 16.8. He is tall and lanky. Extremities were notable for some telescoping of his fingers. Upper extremities and lower extremities were normal except that he could collapse his hands and he could almost touch his thumb to his volar surface. He had pes planus and mild hyperextensibility at his elbows and at his knees.

Labs include: 5-OH Vitamin D 9, TSH 1.1, Total Testosterone 636 ng/dL (348-1197), Calcium 9.4, Ionized calcium 1.11, iPTH 44 (11-51 pg/mL), Alk phosphatase 85 mcg/L, 24 urine calcium 26.2, total volume 615 ml. Elevated urine N-Telopeptide 138 (12-99 nmol/mmol), indicative of high bone turnover. Subsequent DEXA scan reveals a bone mineral density (BMD) T-score of -3.3 of the AP Spine, -1.9 of the femoral neck, and -1.9 of the total hips, indicative of low BMD for the patient's chronological age.

Further questioning reveals an extensive family history of fractures and osteoporosis. His mother had a hip fracture secondary to a fall at the age of 46. His grandfather had a hip fracture in his 80's. Multiple aunts and cousins have osteoporosis. Due to a strong family history, the patient was presumed to have an autosomal-dominant osteoporosis, with a connective tissue component similar to Ehlers-Danlos. The patient was sent to genetics for further evaluation. The patient was considered for pharmacological bisphosphonate therapy, however, due to his age and weight gain, nutritional treatment was initially trialed. The patient continues Vitamin D 50,000 IU and Calcium 500 mg once daily.

This case illustrates the diagnostic criteria, genetics, and treatment of primary autosomal dominant osteoporosis.

Discussion

Diagnosis

Osteoporosis is a skeletal disorder of reduced bone strength and increased fracture risk. This condition has generally been considered an adult disease, but osteoporosis which is symptomatic during childhood is emerging as a newly recognized problem.[1] Primary osteoporosis, occurring in young and middle-aged patients is rare and poorly described.[2] Pediatric osteoporosis is defined by the International Society for Clinical Densitometry (ISCD) as (1) clinically significant fracture history defined as the presence of either two or more long bone fractures before the age of 10 years or three or more long bone fractures at any age up to 19 years in combination with bone mineral density (BMD) Z-score ≤ -2; or (2) one or more vertebral compression fractures occurring without high energy trauma or local disease irrespective of the BMD *Z*-score.[3,4] This definition aims to distinguish common fractures of childhood due to non-accidental trauma from children with an underlying condition. However, there are several challenges with this definition. Depending on the reference data used to calculate the BMD *Z*-score, this score can differ by as much as 2 SD,[5,6] which represents the VMD Z-score cut-off of <-2. Another challenge is the risk of underdiagnosis while waiting for subsequential fracture in children with low BMD or in children with BMD *Z*-score above −2 despite recurrent fractures. Ultimately, pediatric osteoporosis is a clinical diagnosis based on severity and underlying disease, and not based on BMD alone.[7]

Genetics

Low BMD is a major component of osteoporosis, influenced by genetic variation and environmental factors.[8] BMD is significantly heritable, with an estimated 60 to 80% in families and twins.[9,10] Similarly, osteoporotic fractures due to low BMD, are heritable with an estimated 50% to 70%.[11,12]

Genome-wide association studies of population-based individuals have revealed several genes associated with low bone mass and risk of fracture.[13] Most forms of childhood-onset primary osteoporosis are termed osteogenesis imperfecta, a vague diagnosis that belongs to a heterogeneous group of skeletal disorders with diverse clinical presentations.[14,15] No consensus indicates which genotype-phenotype combinations should be classified under osteogenesis imperfecta and which should not, further complicating management.[16]

Rare mutations have been reported in young adults with osteoporosis, particularly in cell factors that regulate bone remodeling or extracellular matrix.[17] In 2013, several groups identified WNT1 as a key ligand to the WNT pathway in bone health.[18] Dysregulated WNT/β-catenin signaling leads to various skeletal disorders of low bone mass.[19] Heterozygous WNT1 mutations are reported to cause autosomal dominant osteoporosis.[20]

One of the most recently identified forms of monogenic osteoporosis is caused by mutations in the PLS3 gene,[21-25] encoding the actin-binding, actin-bundling protein plastin 3. This primary early-onset osteoporosis is characterized by low BMD, severe thoracic kyphosis, and frequent peripheral and vertebral compression fractures. While the role of PLS3 in bone fragility is yet unknown, there are several theories regarding its role from mouse studies. Current studies suggest PLS3 may (1) alter osteocyte function through abnormal cytoskeletal microarchitecture; (2) play a role in bone mineralization and (3) cause osteoclast malfunction.[26-28] The total number of diagnosed patients is low and understanding of disease progression and treatment is limited.

Treatment

Conventional osteoporosis drugs, such as bisphosphonates, have been the main pharmacological treatment for OI. Osteoclast-targeting and resorption-decreasing bisphosphonates have proven effective in increasing BMD and reducing fractures.[29,30] Besides WNT1-related skeletal pathologies, even less is known about the optimal treatments in other new forms of primary osteoporosis, such as PLS3.[31] The efficacy of bisphosphonates in PLS3 osteoporosis has been evaluated in limited cases and with a positive effect.[21,22]

Clinical care of OI patients, including monogenic osteoporosis, is complex and challenging. Treatment is dependent on the patient's age, degree of impairment, and clinical findings. Bisphosphonates remain the main treatment for pediatric patients to prevent a greater decrease in BMD and enable maximum yield in bone minerals. Patients with OI require multidisciplinary care and further investigation on treatment and progression.

In summary, osteoporosis in the pediatric and young adult populations is rare. Current diagnostic criteria are in place but may go unrecognized when evaluating pediatric and young adult fractures in the primary care setting. Pathology of this disease has been linked to a dysregulated WNT1 pathway and mutations in the PLS3 gene. Further investigation into the various genetic subtypes of this disease is key to improving treatment and outcomes.

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