INTERDISCIPLINARITY IN OSTEOGENESIS IMPERFECTA

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Abstract: *Osteogenesis imperfecta is a heritable skeletal dysplasia, a generalized disease of the connective tissue, pathological changes being observed in all tissues in which type 1 collagen is an important component. The objective of this report is to highlight interdisciplinary team approach in adults with hereditary conditions, particularly in osteogenesis imperfecta type I. We report the case of a 54 year-old female patient, hospitalized for polyarthralgias, joint stiffness of the left elbow, right fist, left knee and functional disability. She has short stature, a history of multiple minor impact fragility fractures, hearing loss, cardio vascular manifestations, hip osteoarthritis, early menopause, chronic venous disease. The long term goal of pharmacological treatment and medical rehabilitation is functional independence. Physical, kinetic and occupational therapy can help the patient to maximize the activities, thus overcoming functional limitations. Case management requires a multidisciplinary team approach.*

INTRODUCTION

Osteogenesis imperfecta, or brittle bone disease is a heritable skeletal dysplasia, a generalized disease of the connective tissue, pathological changes being observed in all tissues in which type 1 collagen is an important component, such as bones, ligaments, dentin and sclera. Type 1 collagen deficit may be quantitative or qualitative. Mutations affecting the genes encoding pro-α1 or pro-α2 chains of type I collagen account for more than 90% of osteogenesis imperfecta cases.(1) More than 1 500 dominant mutations in these genes have been identified. The resulting phenotype is variable, ranging from mildly affected, leading to subclinical forms, to lethal forms.(2)

Osteogenesis imperfecta is considered a rare disease, the prevalence being estimated at 1/10 000 and 1/20 000.(3) Morbidity and mortality in osteogenesis imperfecta cases depend on the genotype. They are mostly related to respiratory and cardiovascular manifestations. A clinical and echocardiographic survey aimed at investigating cardiac abnormalities in adults with osteogenesis imperfecta revealed that hypertension was diagnosed in 37 cases (37.4%). Affected adults had increased left ventricle mass, mitral regurgitation and aortic regurgitation compared to the control group.(4,5) Other non-skeletal features associated with osteogenesis imperfecta are neurological problems, hearing loss, dental abnormalities.(5) Several general rules for genotype phenotype correlation in cases with the autosomal dominant forms have been proposed, but it is known that exceptions may occur and all these are important for the genetic counselling.(6,7)

Initially, osteogenesis imperfecta was classified in four types according to clinical and radiologic findings and severity of the disease (8), this classification being expanded with other four types.(9,10) A new classification that underlines the importance of phenotyping for the diagnosis was more recently proposed. Clinical features together with specific molecular genetic causes will be the basis for the management of each case.(11) Until recently, the main therapeutic options for osteogenesis imperfecta were surgery, physiotherapy and orthotic support.(12) With a deeper understanding of the disease molecular mechanisms, medical treatment used to increase bone mass and bone strength has gained popularity. Drugs like bisphosphonate, pamidronate, strontium ranelate which inhibit osteoclast mediated bone resorption, significantly improve the prognosis of the disease, by decreasing fracture frequency, increasing bone density, decreasing bone pain.(13-16)

Majority of the reports and research to date were focused on children with osteogenesis imperfecta. Affected adults might have comorbidities or different factors associated with aging and injuries, thus case management will have some particular aspects.(17)

The objective of this report is to highlight interdisciplinary team approach in adults with hereditary conditions, particularly in osteogenesis imperfecta type I.

CASE REPORT

We report the case of a 54 year-old female patient, of urban environment, hospitalized for treatment and functional rehabilitation in the Medical Rehabilitation Clinical Hospital "Băile Felix", Romania. She was born from healthy, unrelated parents and the family history was negative. The patient's complains at admission in our hospital were polyarthralgias, joint stiffness of the left elbow, right fist, left knee, muscle and bone pain and functional disability.

Personal history of the patient revealed that she had multiple minor impact fragility fractures which started during childhood: distal 1/3rd of the right humerus and right radius, healed with vicious callus that led to elbow deformity at 6 years old; 1/3 middle of the right femur at 6 years old; proximal shaft of the left femur at 32 years old; left cubitus and radius and superior 1/3 of the left tibia at 47 years old; left tibial plateau - left patella at 51 years old; right ulna and radius fracture at 52 years old. She reported early menopause at 36 years of age. Cardio vascular diseases were hypertension, which was diagnosed at the age of 42 years and degenerative mitral insufficiency for which she had surgery four years ago. Hip

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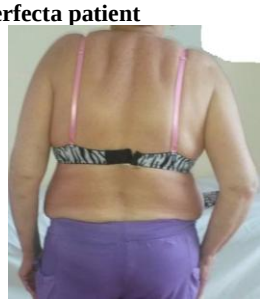
osteoarthritis diagnosis was established at 48 years of age. She also had post-thrombotic syndrome in the left leg diagnosed twelve years ago and a bone cyst of the left calcaneus operated two years ago.

The patient had short stature, her height was 159 cm, the weight was 63 kg and the body mass index (BMI) was 24.9. Physical examination revealed holosystolic mitral murmur at the apex, radiating to the axilla and the base, strong third heart sound, blue sclera (figure no. 1). Skeletal abnormalities were kyphoscoliosis and barrel-shaped chest, lumbar hyperlordosis, flexum of the left elbow (figure no. 2), genu varum, deformed left foot with antalgic limited mobility, limitations in lumbar spine mobility with modified Schober index: 10/12 and limited extension. Limitations in hip mobility as revealed by internal rotation right hip joint 5^o and left hip joint 8^o, external rotation right hip joint 12^o and left hip joint 15^o, and knee mobilization crepitus were other clinical findings. Ear, Nose and Throat Examination (ENT) revealed hearing loss.

Figure no. 1. Blue sclera in osteogenesis imperfecta patient

Figure no. 2. Vertebral column abnormalities present in osteogenesis imperfecta patient



Laboratory investigations were made, complete blood count revealed normal values and markers of inflammation were also normal. Urinalysis revealed frequent leukocytes, crystals of calcium oxalate and uric acid. Urine culture demonstrated urinary tract infection with E. coli.

Other investigations:

- dual-energy X-ray absorptiometry scan (DXA) showed diffuse osteoporosis, lumbar spine T score - 4.7, left hip T score -3.9 and right hip T score - 2.7.
- pelvic radiograph revealed hip osteoarthritis grade ¾
- echocardiography revealed systolic mitral regurgitation
- abdominal ultrasound showed the presence of renal microlithiasis

Based on the medical history with early onset and frequent fractures after minor trauma, on the clinical findings with short stature, kyphoscoliosis, barrel-shaped chest, blue sclera, cardiovascular manifestations, hearing loss together with data from the other investigations, the following diagnoses were established: Osteogenesis imperfecta type I. Bilateral hip osteoarthritis grade 3/4, with painful and functional decompensation. Algofunctional sequelae of the left leg after surgery for calcaneal bone cyst. Lower-extremity venous disease C3 (Clinical-Etiology-Anatomy-Pathophysiology - CEAP classification). Stage two hypertension. Operated degenerative mitral insufficiency. The therapeutic plan follows the multidisciplinary team assessment of this case. The treatment aimed at: relieving pain; re-educating lower trunk stability; recovering mobility; preventing falls; maintaining blood pressure within normal values; preventing progression of the venous disease. Therapeutic means: life-style changes with reduced dietary salt and increased dietary calcium intake or increased intake of calcium and vitamin D.

Pharmacological measures include some medications with evidence of efficacy on major fractures, with solid clinical trials, taking into account side effects. Monitoring treatment is compulsory and there are precise terms for patient monitoring.

Other medications are needed for the hypotensive effect, chondroprotection and venotonic therapy. Balneo-physical therapy used procedures with painkiller effect: laser, electrotherapy, massage. Lymphatic drainage aimed venous and lymphatic circulation improvement. Hydrokinetotherapy at 36^o C for 20 minutes, water heat relieving pain and leading to muscle relaxation. Strict blood pressure monitoring was recommended for this procedure. Kinetic therapy aimed at improving mobility and stability of all joints. Fall prevention learning is particularly important for patients' training and preventing fractures.

Kinetic therapy aimed at improving: legs posture and thus, venous-lymphatic circulation; spinal posture for the re-education of kyphoscoliosis; lower trunk posture to reduce lower body deformations; mobilization of all joints with emphasis on the spine and lower train; toning abdominal muscles, quadriceps, gluteus medius, triceps surae muscles.

Another important objective of kinetic therapy was preventing falls. Stability of the body increases with increasing muscle strength. This is achieved primarily by means of walking and coordination exercises. All these exercises can be learned and repeated daily. These exercises are: climbing stairs, avoiding obstacles, ball games, performing dance steps.

In conclusion, the use of all types of exercises together will give the best results. The long term goal of pharmacological treatment and medical rehabilitation is functional independence. This can be achieved by: protective postures, protected movements, hydrothermotherapy. Physical, kinetic and occupational therapy can help patients to maximize the activities, thus overcoming functional limitations.

The peculiarity of the case is represented by the increased number of fractures during adulthood, usually the number of fractures decreases in adulthood. This could be also a consequence of the early menopause, which installed at 36 years of age.

DISCUSSIONS

Osteogenesis imperfecta comprises a group of genetic disorders that are characterized by a heterogeneous spectrum of clinical features, such as fractures that occur spontaneously or with minimal trauma, limb deformities, joint laxity, skeletal abnormalities, blue sclera, deafness, dentinogenesis imperfecta, growth retardation. The disorder is not only clinically but also genetically heterogeneous. The genetic complexity of its molecular bases, new mutations that have been described and the variation of the clinical manifestations led to discussions regarding the classification of the disease. One approach is that Sillence classification is usually the prototype for classifying osteogenesis imperfecta according to the severity, from the clinical point of view, and the mutations of the genes are listed separately.(11,18,19)

The clinical diagnosis is now confirmed by molecular testing. Laboratory diagnostic can establish the existence of decreased or abnormal production of collagen and the existence of mutations in *COL1A1* and *COL1A2* genes, which are responsible for the vast majority of affected cases, or in other genes, which account for less than 10% of all cases.(20)

Osteogenesis imperfecta type I is the most common form and it is the mildest type. Patients have variable degrees of bone fragility, moderate deformation of bones, blue sclera, and

early hearing loss.(19) Many earlier studies have focused on diagnosis and treatment of osteogenesis imperfecta in children (21-23), but more recent ones publish data regarding molecular, clinical and therapeutic aspects also in adults.(24-26) An accurate diagnosis is both essential for the management of the case and for genetic counselling. Genetic counselling is offered to the affected individual or family members.

Management of affected individuals is multidisciplinary. It requires evaluation of the musculoskeletal system, cardio-vascular and respiratory systems, hearing and ophthalmologic evaluation. Therapy aims at decreasing the number of fractures, preventing falls, preventing deformities, minimizing pain and functional disability. Therapy means are represented by life-style changes, medication, surgical correction of deformities, medical rehabilitation. Medication introduced early during infancy or childhood together with physical and occupational therapy, has reduced fracture frequency by up to 50%.(27) A population-based study aiming to assess the ability to perform activities of daily living (ADL) in osteogenesis imperfecta patients revealed that most of them were able to live an independent life, but the severity of the disease had influenced their abilities.(28)

CONCLUSIONS

1. Osteogenesis imperfecta is underdiagnosed in our country. Early diagnosis can be facilitated by personal and family history, clinical examination and imaging.
2. Case management requires a multidisciplinary team approach, focusing on preventing fractures, minimizing deformities, obtaining optimal bone mass and muscle strength in order to improve quality of life.

REFERENCES

1. Basel D, Steiner RD. Osteogenesis imperfecta: recent findings shed new light on this once well-understood condition. Genet Med. 2009;11:375-85.
2. Marini JC, Forlino A, Cabral WA, Barnes AM, San Antonio JD, Milgrom S, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. Hum Mutat. 2007;28:209-21.
3. http://www.orpha.net.
4. Radunovic Z, Wekre LL, Diep LM, Steine K. Cardiovascular abnormalities in adults with osteogenesis imperfecta. Am Heart J. 2011;161(3):523.
5. Forlino A, Cabral WA., Barnes AM., Marini JC. New Perspectives on Osteogenesis Imperfecta. Nat Rev Endocrinol. 2011;7(9):540-57.
6. Ben Amor IM, Glorieux FH, Rauch F. Genotype-phenotype correlations in autosomal dominant osteogenesis imperfecta. J Osteoporos. 2011:540178.
7. Ben Amor IM, Roughley P, Glorieux FH, Rauch F. Skeletal clinical characteristics of osteogenesis imperfecta caused by haploinsufficiency mutations in COL1A1. J Bone Miner Res. 2013;28(9):2001-7.
8. Silence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101-16.
9. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004;363(9418): 1377-85.
10. Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S, et al. Prolyl 3 -Guide to Osteogenesis Imperfecta for Pediatricians and Family Practice Physicians 27 hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. Nature Genetics. 2007;39(3):359-65.
11. Van Dijk FS, Sillence DO. 2014. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet Part A 321A*:*1470-81.
12. Jones D, Hosalkar H, Jones S. The orthopaedic management of osteogenesis imperfecta. Clin Orthop. 2002;16:374-88.
13. Shapiro JR, Thompson CB, Wu Y, Nunes M, Gillen C. Bone Mineral Density and Fracture Rate in Response to Intravenous and Oral Bisphosphonates in Adult Osteogenesis Imperfecta. Calcif Tissue Int. 2010;87(2):120-29.
14. Kusumi K, Ayoob R, Bowden SA, Ingraham S, Mahan JD. Beneficial effects of intravenous pamidronate treatment in children with osteogenesis imperfecta under 24 months of age. J Bone Miner Metab. Oct 16 2014.
15. Hald JD, Evangelou E, Langdahl BL, Ralston SH. Bisphosphonates for the Prevention of Fractures in Osteogenesis Imperfecta: Meta-Analysis of Placebo-Controlled Trials. J Bone Miner Res. Nov 18; 2014.
16. Orwoll ES, Martin E. Pharmacologic Treatment of Osteogenesis Imperfecta. In Shapiro JR, Byers PH, Glorieux FH, Sponsellor PD, editors**.** Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease, Amsterdam: Elsevier/Academic Press; 1 edition. 2013:519-25.
17. Trovato MK, Schultz SC, Joseph C. Physical Medicine and Rehabilitation. In Shapiro JR, Byers PH, Glorieux FH, Sponsellor PD, editors**.** Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease, Amsterdam: Elsevier/Academic Press; 1 edition. 2013:485-91.
18. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155A(5):943-68.
19. Valadares ER, Carneiro TB, Santos PM, Oliveira AC, Zabel B. What is new in genetics and osteogenesis imperfecta classification? Jornal de Pediatria. 2014;90(6):536-41
20. van Dijk FS, Byers PH, Dalgleish R, Malfait F, Maugeri A, Rohrbach M, Symoens S, Sistermans EA, Pals G. EMQN best practice guidelines for the laboratory diagnosis of osteogenesis imperfecta. Eur J Hum Genet. 2012;20:11-9.
21. Forin V. Paediatric osteogenesis imperfecta: medical and physical treatment. Arch Pediatr. 2008;15(5):792-3.
22. Bishop N, Adami S, Ahmed SF, Antón J, Arundel P, Burren CP, et al. Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382(9902):1424-32.
23. Castillo H, Samson-Fang L. Effects of bisphosphonates in children with osteogenesis imperfecta: an AACPDM systematic review. Dev Med Child Neurol. 2009;51(1):17-29.
24. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2014; 7:CD005088.
25. Van Dijk FS, Huizer M, Kariminejad A, Marcelis CL, Plomp AS, Terhal PA et al. Complete COL1A1 allele deletions in osteogenesis imperfecta. Genet Med. 2010;12:736-41.
26. Van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PGJ, van Rijn RR et al. Osteogenesis imperfecta: a review with clinical examples. Mol Syndromol. 2011;2:1-20.
27. Bishop N. Characterising and treating osteogenesis imperfecta. Early Hum Dev. 2010;86(11):743.
28. Wekre LL, Frøslie KF, Haugen L, Falch JA. A study of demographical variables and ability to perform activities of daily living in adults with osteogenesis imperfecta. Disabil Rehabil. 2010;32(7):579-87.