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ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

HELLENIC ASSOCIATION
OF ORTHOPAEDIC SURGERY
AND TRAUMATOLOGY

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- **Letters to the editor:** Communication to the editor is welcomed and will be published if they offer pertinent and/ or constructive comment on articles published in the Acta Orthopaedica Et Traumatologica Hellenica. Letters are published at the discretion of the Editorial team and should be received within three months after on-line publication of an article. Following acceptance, letters will be sent to authors for response. Letter communications should include text of no more than 500 words, up to 2 figures and 10 references, without any abstract or keywords and a maximum of 3 authors.

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Figures need to be of high quality. Vector graphics, scanned line drawings and line drawings need to be in bitmap format and should have a minimum resolution of 1,200 dpi. Halftones (photographs, drawings or paintings) need to be in TIFF or JPEG format, up to 174 mm wide and up to 234 mm high and in minimum resolution of 300 dpi.

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or

Papaioannou NA, Triantafyllopoulos IK, Khaldi L, et al. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis Cartilage* 2007; 15(4): 386-95.

■ Book chapters:

Triantafyllopoulos IK, Papaioannou NA. The Effect of Pharmacological Agents on the Bone-Implant Interface. In: Karachalios Th. (ed). Bone-Implant Interface in Orthopaedic Surgery. Springer – Verlag, London 2014, pp 221-237.

■ Online document:

National Institute for Health and Care Excellence. Fractures (Complex): Assessment and Management. Available via www.nice.org.uk/guidance/ng37. Published Feb 2016. Updated Sept 2017. Accessed January 2014.

12. Review of manuscripts

Acceptance of manuscripts for publication is decided by the Editor, based on the results of peer review. Authors need to make proof corrections within 72 hours upon pdf supplied, check the integrity of the text, accept any grammar or spelling changes and check if all the Tables and Figures are included and properly numbered. Once the publication is online, no further changes can be made. Further changes can only be published in form of Erratum.

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Chronic Congenital Hyperphosphatasia (Juvenile Paget's Disease) - A Review

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ABSTRACT

Chronic Congenital Hyperphosphatasia (or «Juvenile Paget's Disease") is an exceptionally rare bone disease, which registers currently just over fifty cases in worldwide literature. It is an inherited skeletal disorder, with very early onset, extremely high bone turnover and bone mineralization disorders that affects the whole skeleton. This review examines the published case reports to date and focuses on the pathogenesis, clinical features, epidemiology, diagnosis and therapeutic approaches of the disease.

KEY WORDS: Hyperphosphatasia, Juvenile, Paget, Pathogenesis, Treatment

1. Introduction

The term «hyperphosphatasia» or «hyperphosphatemia» describes the elevation in both alkaline phosphatase (ALP) serum levels and enzyme activity beyond normal levels. Hyperphosphatasia applies to many normal and pathological conditions such as skeletal growth, pregnancy, liver and bile duct diseases, endocrine diseases like acromegaly and hyperparathyroism, bone fractures and metabolic bone diseases such as Paget disease, osteomalacia, bone tumors, osteogenesis imperfecta, fibrous dysplasia and, of course, chronic congenital hyperphosphatasia (CCH). [1,2] Obviously, CCH receives its name from the above-mentioned laboratory finding that is due to the extremely high rate of bone turnover affecting both bone formation and resorption. Bakwin and Eiger first presented the disease as a separate clinical entity in 1956. Since then CCH has been described with numerous names like "juvenile Paget's disease", "chronic (or congenital, or familial) idiopathic hyperphosphatasia", "familial osteoectasia with macrocephaly", "inherited hyperphosphatasia" and "skeletal dysplasia with hyperphosphatemia." [3-5]. Clinically, it concerns a generalized skeletal disorder that appears in the first two years of life and leads to the disruption of normal bone growth and maturation, with consequently severe and time-developing bone deformities, increased vertebral and long bones

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fracture liability, as well as the onset of related complications from other systems.

2. Methods

In order to carry out this research, we reviewed the international literature from 1956 to 2019 via the PubMed database. As keywords, we used the terms: Hyperphosphatasia AND Juvenile Paget AND Chronic Hyperphosphatasia AND Idiopathic Hyperphosphatasia AND Clinical features, Epidemiology, Etiology, Pathogenesis, Diagnosis, Management, Treatment, Bisphosphonates, Denosumab, Prognosis. We focused on eighteen case report articles, twenty interventional trials and thirteen older reviews pertaining to the clinical features, epidemiology, pathogenesis, diagnosis and treatment of CCH.

3. Epidemiology

CCH can be classified as an exceptionally rare metabolic bone disease of childhood that currently registers only 56 cases worldwide. The first clinical manifestations occur a few months after birth. The disease itself seems to have no preference for gender or race/ethnicity. Moreover, despite the lack of an established geographical distribution, a significant number of patients have been reported in Puerto Rico child population as well as the Balkan, including Greece. Even more, the disease shows an increased frequency in societies where marriage between close relatives is widespread. [6,7]

4. Pathophysiology

4.1. The role of Osteoprotegerin:

The inherited deficiency of osteoprotegerin activity is essentially the basis of CCH pathophysiology. Osteoprotegerin (OPG) represents a soluble glycoprotein that belongs to the Tumor Necrosis Factor (TNF) Receptor superfamily and is secreted by osteoblasts and osteogenic stromal cells. It carries out its action by forming homodimeric complexes, which act as deactivating receptors of Receptor Activator of Nuclear factor kappa-B Ligand (RANKL), an action that has regulatory effect in bone remodeling, thus protecting bones from excess bone resorption. Another significant and parallel action of OPG is the vascular protection against intense calcification. [1,2,4,8-10] The human gene that encodes OPG is known as TNFRSF11B, it is located on the long arm of chromosome 8 at position 8q24a and consists of five exons and four introns. Numerous cytokines and hormonal factors regulate the gene expression in osteoblastic line cells, either enhancing (interleukin-1β, TNFα, vitamin-D) or inhibiting (glucocorticoids, prostaglandin-E2) protein secretion. [11] There is experimental and clinical proof that the reduced or absent activity of OPG is responsible for the development of high-turnover osteoporosis, as well as of calcifications of the tunica media of large elastic arteries. [10]

In CCH, due to the reduced - or absent - OPG action, high concentrations of active RANKL remain in circulation and bone tissue, resulting in an uninterrupted RANKL-RANK interaction. This phenomenon accelerates immensely bone resorption, which leads to a secondary increase of bone formation. Because of the high rate of bone turnover the membranous bone formation becomes impaired and the bone matrix fails to develop in normal hard and compact haversian bone, producing a generalized skeletal disorder. [4,6,12,13] The result is the excessive production of immature cortical and cancellous bone, which is responsible for bone thickening in the skull and other parts of the skeleton. [6,12] Moreover, bone resorption is relatively higher than formation, which leads in failure of complete osteolytic lesions recovery, resulting in gradual thinning of the bone trabeculae and cancellous bone weakening. The intertrabecular space also enlarges over time and gets filled with loose connective tissue and adipocytes. Although the mineralization rate of the osteoid remains normal, excessive production of newly formed bone results in the development of multiple under-mineralized bone areas. [6,13,14] The abnormal bone resulting from these procedures is called "woven-bone", is characterized by significantly lower quality and strength than healthy bone and resembles to affected bone lesion in Paget's disease. [6,7,12,14]

4.2. Heredity

CCH is the first hereditary human disease described

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as a result of OPG gene mutations and appears to be transmitted mostly with the autosomal recessive inheritance pattern. However, models of autosomal dominant heredity have also been proposed from time to time, and any correlation with sex-related heredity has been excluded. [6,15] Genetically speaking, the responsible impaired gene is TNFRSF11B and approximately 60% of CCH phenotype positive cases are patients with homozygous inactivating gene mutations. The mutations affect the four cysteine-rich extracellular domains (I-IV) of OPG molecule, which are encoded by exons 2 and 3 and represent critical areas for ligand binding and consequently, protein activity. [4,7,16-18] The mutations detected so far in the genome of CCH patients show variety such as missense mutations, frameshift mutation, base insertion and deletion, or even entire TNFRSF11B gene deletion. [4,7,17] The clinical manifestations and phenotype is relevant to the type of mutation. Thus, in cases of a simple addition or deletion of a few bases, the serum levels of OPG remain practically normal, once the production of the mutated protein is normal but the protein has reduced binding activity. The mutations generating amino-acid addition or deletion at the carboxyl-terminal end of the molecule are correlated with the mildest phenotypes of the disease. Missense mutations that do not affect cysteine sequences related to ligand-binding areas of OPG demonstrate medium severity phenotypes. Finally, total gene TNFRSF11B deletion - a state at which OPG levels are undetectable and protein activity absent - corresponds to the most severe phenotype of the disease. [4,5,7,16,18-20]

All the above information explains adequately the clinical manifestations of CCH in most cases. However, there is a small but significant percentage of the patients - less than 40% with milder clinical image - in which no mutation nor TNFRSF11B gene deletion can be detected and the underlining cause remains undefined. [4,7,17] The existence of those CCH case reports suggests that the etiopathogenesis of CCH is more complicated and has not yet been fully elucidated. Nonetheless, some authors support the possibility of misclassification due to clinical similarities with other conditions such as polyostotic fibrous dysplasia or familial expansile osteolysis. [7,16,19]

5. Clinical Image

5.1. Clinical manifestations:

CCH is a serious clinical entity that affects the entire skeleton. The severe bone lesions are time-aggravating and occur mostly during skeletal growth and until skeletal maturation. The impaired bone quality affects negatively the human functionality and therefore the quality of life of the patients.

5.1.1. Skeletal deformities:

The dominant clinical manifestations of CCH are bone anomalies and deformities. They are bilateral, symmetrical and progressive and always present throughout the skeleton. All the long bones, including the finger and toe phalanges, develop cortical thickening with the diaphysis being the most affected area of the bone. The consequence is intense diaphyseal deformities that lead to shorter than normal bone length. The reduced bone strength in addition to the insufficient mineralization produce the characteristic diaphyseal anterolateral bowing. Coxa vara and acetabular protrusion are two other frequent complications of CCH. [6,21] The skull is another bone complex that develops overgrowing lesions, specifically the diploe which appears sclerotic and enlarged. The development of macrocephaly with hypertelorism although disease characteristic is not always present and usually is observed in children of older age. Very rarely coexists aplasia or dysplasia of the paranasal cavities, mostly the maxillary, the frontal and the sphenoid sinuses. [6,20] As far as the dentition is concerned, adult teeth appear normal, however they delay significantly to erupt. Regarding the primary dentition, there is frequent premature loss of deciduous teeth. [12,22,23] Spinal deformities contribute often and severely to the clinical picture, through the development of osteopenia or osteoporosis, vertebral subsidence, or even kyphosis and/or scoliosis. The chest wall and the pelvis also demonstrate dysplastic lesions deformities, with major representative the pectus carinatum. [24,25]

Due to the presence of severe bone deformities, the patient's growth rate gets impaired resulting in low stature below the 3rd percentile position on the corresponding growth charts to gender and height. Bone pain, headache and increased spontaneous fracture

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risk represent concomitant manifestations and complication of CCH. Fractures are usually multiple and most often complicate children with less severe phenotypes. This incident can be explained by those patients ability to be more active and have better mobility and therefore to have increased likelihood to suffer falls and injuries. [7,15] As far as walking ability, the impairment of the gait shows variety being relevant to the severity of the disease. The children usually delay to conquer walking and they have an ungainly gait. Sometimes walking is not obtained at all or obtained over a short period of time and then lost. In other, milder, cases the ability to walk may remain intact. [23-25]

5.1.2. Neurological and sensory complications:

On the ground of CCH, nerve foraminal stenoses with consequential neurological and sensory disorders are a common occurrence deteriorating with aging. The stenoses develop as a result of the overproduction of the pathological bone near the cranial foramina, gradually filling the foraminal space entrapping the passing nerves and causing from nerve compression up to nerve paralysis. All the cranial nerves may be affected through the same mechanism, but the cochlear and optical are predominately the nerves that are implicated. [21] Thus, the patients often exhibit bilateral hearing loss, typically established before puberty, which is due to cochlear nerve impairment. Especially for hearing loss, other causes apart from inner ear bone stenosis have been mentioned occasionally, such us the congenital auditorial ossicle absence, eardrum thickening and extra bone masses in the middle ear derived from bone overgrowth. [20-22,26]

Severe visual disorders also start to appear around the end of puberty and have already been described in twelve of the fifty-six patients that have been reported worldwide with CCH. The most harmful condition is the progressive blindness due to optical nerve atrophy. Clinical findings from the eyes that occur with increased incidence in CCH include the gradually progressive retinitis pigmentosa, visual field restriction, central vision black spots, choroidal neovascularization, macular degeneration and angioid streaks. The last ones are recognized as ruptures of a thickened and calcified Bruch's membrane and represent the most common pathological finding from the eye in patients. [6,21,23,27] The exact formation pathway is yet to be determined. However, it is speculated that in the absence of normal OPG activity there is a predisposition for calcification of the elastin-rich elastic layer of the Bruch's membrane. [27]

5.1.3. Vascular complications:

One of the most compounding factors concerning the prognosis of patients with CCH is the increased incidence of concomitant vascular disorders, the most common of which are arterial hypertension and elastic pseudoxanthoma. Worth mentioning is a CCH case of an 18year old teenager with concomitant severe angiopathy that passed away succumbing to an extensive stroke. [6] Arterial hypertension has been reported in a relatively large number of patients. Elastic pseudoxanthoma, on the other hand, is one of the less frequent complications of the disease and is rather observed in older patients. It regards progressive, aggravating calcification of tissues rich in elastin, such as the middle and inner layer of elastic blood vessels. Coronary heart disease and renal artery occlusion are two of the primary consequences resulting from this specific pathological process. [23] Considering the mechanism, it is mentioned that the smooth muscle fibers and the endothelial cells of the arteries secrete RANKL in both the atherosclerotic plaque and blood circulation. Therefore, it is most likely that due to the inadequate action of OPG in CCH, the negative effects of RANKL on the blood vessels can not be sufficiently controlled. [28,29]

5.1.4. Other complications:

Beyond the above mentioned major clinical manifestations, the patients with CCH often experience low-threshold fatigue and progressively worsening muscle weakness, accompanied by muscle limb atrophy, sometimes to such an extent that the affected persons can not even sit down. Atrophy and painful swelling of periostotic soft tissues generally coexist. Additionally, the disease has also been linked to a relatively high incidence of nephrolithiasis. [12,21,24] Finally, the majority of the authors support the state-

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ment that the age of puberty's onset and mental status remain in normal range. Only exception to the last is the reduced learning capacity that the patients with neurosensory loss of hearing demonstrate, a condition though that falls in to frame of hearing disability and impaired aural comprehension. [6,7,14,23]

5.2. Time of clinical onset of CCH:

Generally, the onset of the disease and the time of diagnosis shift to earlier age as more severe becomes the mutation of OPG gene. The patients appear healthy at birth, but further on, they gradually develop the skeletal deformities mentioned above. At first, they always develop the long bone lesions as the primary disease manifestation and later on the concomitant disorders that regard child development and growth. Most commonly, the disease appears between 3 and 18 months of age but the diagnosis is put around toddlerhood until early preschool age, a time when the signs and symptoms have become clearly obvious. Rarely, in the mildest cases, the disease can be diagnosed in late childhood. [7,12]

5.3. Severity of the disease:

The severity of clinical manifestations of CCH vary significantly from patient to patient and is relevant to the degree that the genetic lesion affects the activity of OPG. In most cases the clinical image is severe, leading to serious bone lesions and complications. In general, the clinical phenotypes of the patients can be grossly classified as follows: [7,30]

- **Severe:** The bone deformities begin to be recognized during the first 18 months of life, while the child fails to conquer walking ability. Even if the patient manages sometime to walk, this happens markedly late and eventually gets lost during the early childhood.
- **Moderate:** Skeletal deformities occur later, approximately two years after birth, and the child begins walking at normal age. However, bone lesions are progressively aggravated, causing a steadily lower stature below the 3rd percentile position on growth charts according to gender and age.
- **Mild:** The bone lesions begin after the second year of life. Patients pertain a satisfying mobility, while their stature remains within normal limits.

The severity of clinical manifestations is further influenced by two separate parameters, regardless of phenotype: The first is the age, as bone deformities develop gradually and affect mostly patients in puberty and adolescence or older ages. The second factor is the anti-osteoclastic therapy administered to CCH individuals, as the successful application of treatment can greatly influence the progression of CCH and its final clinical image. [7]

6. Imaging assessment

The usually severe clinical presentation of CCH, with the extended skull, body and limb deformities, predicts the findings from the imaging assessment of the patients. It is essential to make the remark that the radiological image of the patients with mild or moderate phenotypes of CCH is in basically better that those with severe disease forms. Only exception to that are the pathological fractures that occur most frequently to more ambulatory patients. [6,7,31]

(a) Simple X-rays. In the severe cases of the disease - especially when macrocephaly is present - the bones of the skull appear thickened and enlarged. The diploic space is distended and the mastoid processes loose their natural pneumatic appearance. These lesions develop symmetrically and progress over time. [12] The paranasal sinuses are often hypoplastic (or rarely aplastic), while the "cotton wool" appearance of the skull - representing multiple localized spots due to the coexistence of osteopyknotic and osteolytic lesions - is very common. [6,24] The rest of the bones show predominately osteopenia combined with osteosclerotic areas. Trabecular bone has a rough and irregular appearance, while cortical bone is quite thick, although there are areas extremely thin like "paper". The spine usually consists of biconvex vertebrae with reduced height. The intervertebral spaces are increased and the whole backbone receives deformities like scoliosis, kyphosis and lordosis. [32,33] The long bone lesions regard mainly the excessive diaphyseal widening in comparison to the normal appearing epiphyses, the development of bowing, the marked cortical thickening of the femur-medial cortex and the occurrence of multiple fractures. Transverse lines through the area

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of the diaphysis are quite often and represent locations of vascular micro-infarctions. Acetabular protrusion and coxa vara are two more common radiological findings. [7,12,23,25,31,33] The ribs, the scapula and clavicle share similar deformities, having enlarged dimensions with the presence of areas of increased and decreased bone density. [6,12,25,31]

(b) Cross-sectional imaging assessment. Evaluation via computed tomography (CT) or magnetic resonance imaging (MRI) is more adequate to diagnose lesions that cause nerve compression or other complications due to the overwhelming bone growth. Typical example is the cranial or spinal foraminal narrowing, causing nerve entrapment and the consequent sensory and neural deficits. [21]

(c) Bone Scintigraphy. In CCH patients bone scan is not considered to be an essential examination to perform. Only two cases in the past were submitted to bone scan, which produced diffused and increased uptake of the radioactive agent throughout the entire skeleton. [21]

7. Laboratory findings

Beyond the clinical and imaging particularities of CCH, an important and critical role in diagnosing the disease has the laboratory evaluation, which reflects the markedly increased bone turnover of the patients. Thus, the serum levels of ALP (total and bone fraction), measure five to ten time above the upper limits of normal ranges, a finding that is caused by the increased osteoblastic activity. That extend of ALP elevation is a main element and rule in the disease. [21,24,25] However, scarcely though, in sporadic CCH cases with mild phenotype, ALP levels have been observed to be just above the higher limits or within the normal ranges of the enzyme. Nonetheless, a correlation between the severity of the clinical phenotype and the degree of elevation of serum ALP has not been established. [6,7] Apart from ALP, other enzymes are also traced in pathologically elevated concentrations in serum (such as acid phosphatase and leukine aminopeptidase) [21,22,34] as well as type-I collagen degradation products that are determined in urine [such as amino-terminal collagen crosslinks (NTX), carboxyl-terminal collagen crosslinks (CTX) and proline], due to the overactivity of the osteoclasts. [13,24] Regarding the blood concentrations of calcium, phosphorus and magnesium, they remain always within normal range of values. Serum levels of uric acid can be within normal values, or slightly elevated probably due to the cellular overactivity. Finally, hypercalciuria or/and hyperuricosuria are mentioned relatively frequently, although there were some cases with 24hour urinary calcium concentrations below normal. [7,24,34]

8. Anatomical pathology data

The histological findings reflect the disturbed bone turnover that characterizes the disease. Typically, there is marked increase in the number and size of the osteoclasts as well as the osteoblasts, but in a lesser degree. Even though the activated osteoclasts enlarge they never reach the typical form of the gigantic multinuclear cells that are met in Paget's disease in adults. [6,7,14,32] Finally, both cortical and cancellous bone are gradually transformed into a matrix of rough, thickened, immature and weak bone (woven bone), the main characteristics of which are the thin trabeculae, the presence of soft connective tissue and adipocytes filling the distended intertrabecular space and the impaired mineralization of osteoid. As a result, the normal haversian systems disappear, fibrosis develops and in the end the affected osseous tissue receives a completely unruly and chaotic structure. [6,13,22,24,35] Thus, the cement lines of the cortical bone are distinct and irregularly distributed, the architecture of the thin trabeculae of the cancellous bone is completely disorganized and surrounded by thick bands of osteoid, while the periosteum shows focal thickening and increase count in cells. [7,13,32]

9. Differential Diagnosis

9.1. Adult Paget's Disease of Bone (PDB)

CCH as a disease bears significant resemblance to PBD, hence the term "juvenile Paget's disease" that had been predominately used in world literature. Nowadays, it has been established that the two diseases are two separate, individual clinical entities. [8] The similarities between them regard mainly to the increased rate of bone turnover, the increased bone fra-

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gility and bowing of long bones of limbs, the intense bone pain, the significant elevation in bone fraction of serum ALP and, mostly, the positive response of both diseases to antiosteoclastic treatment. [7,18,22] Nevertheless, the existing differences are greater and rather more than the similarities. Thus, CCH is diagnosed in infants, toddlers and children while PDB in individuals older than 25 years. Moreover, the bone lesions in the first are generalized and symmetrical, in contradiction with PDB that are more localized and lack symmetry. Macrocephaly, short stature, sensory and vascular disorders as well as dental deficits do not develop in PDB. Finally, the osteosarcoma development has never been reported in CCH, in opposition to PDB. [7,8,12] Histologically, the trabecular bone volume appears diminished in CCH and increased in PDB, while the characteristic gigantic multinuclear osteoclasts are present exclusively in PDB. [8,35,36] Lastly, down to the level of pathogenesis, in PDB there are genetic factors which involve mutations that affect proteins RANK and p62, in addition to environmental influence such as viral infections. On the other hand, CCH is related to an inheritable lack or insufficient action of the OPG protein due to gene TNFRSF11B malfunction. [7,8,18]

9.2. Diseases that are caused by mutations in the TNFRSF11A gene.

The TNFRSF11A gene is located at chromosomal position 18q22.1 and is responsible for the encoding of factor RANK. The diseases that are caused by activating mutations of that particular gene are quite rare, transmitted on to next generations by autosomal dominant inheritance and resemble significantly with the clinical image of CCH, since they also involve the biological pathway of OPG/RANK/RANK, leading in a similar manner to over-activation of osteoclasts. Familial expansile osteolysis, Early-onset Paget's disease and Expansile skeletal hyperphosphatasia are the three known to date genetic disorders that form the specific group of diseases. [8,19,29,37,38]

9.3. Other relevant pathological conditions

There are some pathological conditions of the skeleton that are very alike CCH and have to be included in the differential diagnosis process. These are Rickets, IBMPFD (Inclusion-Body Myopathy, PDB, Frontotemporal Dementia) syndrome, Engelmann's disease, Polyostotic fibrous dysplasia within the McCune-Albright syndrome, type-I Osteogenesis imperfecta, Van Buchem disease, Sclerosteosis, Hyperphosphatasia with mental retardation syndrome, Marbry syndrome, Pyle's disease, Pseudorheumatoied and Spondyloepiphysial dysplasia, Kashin-Beck disease and Transient benign Hyperphosphatasemia. [6,33,34,36-41]

10. Therapeutic Approach

The rare nature of CCH has been an obstacle in acquiring randomized controlled studies, even nowadays, investigating the therapeutic approach of the patients. The first patients in the 1960's received as treatment sodium fluoride, a medication that, although reduced significantly serum ALP values, did not practically improve the clinical image nor did reduce fracture incidence. [32,42] During the following decades, successful treatments were proven to be calcitonin and mainly bisphosphonate agents, which directly act on osteoclasts reducing their excessive activity. As a result, administration of these medications improved laboratory findings and imaging and ameliorate overall the clinical condition of the patients. [7,17,30,43]

Calcitonin treatment was used up until late 1990's in longtime intramuscular, subcutaneous or intranasal administration protocols. At the daily dose of 100 IU calcitonin achieved a 50% reduction of serum ALP levels and a significant pain-relieving effect. It also decelerated disease progression, reduced the number of fractures and improved the quality of patients' life. It's mechanism of action led to a reduction in bone resorption in favor of normal bone formation and to better mineralization, quality and density of bones. [13,14,22,24,42]

Bisphosphonates (BPNs) were firstly introduced in CCH treatment in 1992 by Spindler et al. [44] and continue to be until today the current choice of treatment, since they have proven to be more effective than calcitonin, are generally well tolerated and have a satisfactory safety level even during longtime treatment periods. The prompt administration of in-

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tensified treatment regimens with intravenously (IV) administered bisphosphonates appears to produce the most impressive results, strongly suppressing the rate of bone turnover and therefore preventing the occurrence of bone deformities as much as neurological and sensory complications. [7,17,43] Of all the previously tested protocols, cyclic IV administration of pamidronate appears to be superior. There is evidence supporting its ability to reduce up to 90% serum ALP, restore to normal values the biochemical bone turnover markers, significantly increase bone density, therefore improving in whole the skeleton and eventually promoting child growth. [7,17,43] Adequately good outcome had IV ibandronate in high doses. [30] Zolendronic acid administration has been tried in very few CCH patients but didn't yield good enough results. Elaborating, even though the patients demonstrated significant clinical improvement, serum ALP levels had a lesser reduction in comparison to other IV bisphosphonates. Moreover, the possibility of serious hypocalcaemia after administration was much greater. [43] Regarding the oral administration of BPNs, it is mainly reserved for older children due to better compliance. Etidronate and alendronate have been used in CCH and have yielded positive results regarding clinical condition, histological image and laboratory profile, with a significant drop in serum ALP and urinary hydroxyproline levels. [21,24,36] As a general observation, in CCH no BPN restores the rate of bone remodeling to normal when administered in conventional dosage and this goal can be obtained in most cases only through higher doses. However, due to the lack of relevant studies, specific therapeutic regimens have not yet been defined. [30]

Another promising therapeutic approach is the administration of Denosumab, a monoclonal antibody targeting the RANKL ligand and inhibiting its binding to receptor RANK. To date only three CCH patients have received Denosumab treatment in various schemes, with very good response to bone pain control and bone metabolism markers improvement. [45-47] One of the side effects that must be taken into consideration is the risk of post administration hypocalcaemia in the context of hungry-bone syndrome. Furthermore, the drug influence on CCH complications and the safety profile during long time administration are yet to be identified. In any case, it is also noteworthy that bone resorption inhibitors must be a treatment for life in CCH patients, as any drug discontinuation is always followed by significant reactivation of the disease. [47]

The administration of recombinant OPG could potentially be a satisfactory "replacement treatment" in CCH, however it is not yet used in clinical practice. Experimental administration of the drug, firstly in OPG knock-out mice and secondly in two patients with CCH, resulted in complete suppression of high bone resorption rate, milder reduction of bone formation, increase in cortical bone mass, improvement of radiological imaging and reversal of a large part of the bone pathology of the disease. [17,48] Mild transient symptoms of hypocalcaemia in combination with secondary hyperparathyroidism were also in this case the most important adverse effects. [17,48] It is important to note that due to the mutational nature of the disease, with concomitant OPG gene defect or even absence, it is theoretically possible for patients to develop antibodies against recombinant OPG and then neutralize it. [4,17]

11. Natural History and Prognosis

The high rate of bone remodeling that characterizes CCH continues to fluctuate at abnormal levels for many years after birth, leading to constantly progressive and deteriorating lesions. Therefore, if the disease is not treated timely and adequately, it has a rapid progress in time, with the development of marked bone lesions and complications. The whole progression of CCH often leads to severe disability and shortening of life expectancy to such an extent that the disease can become fatal in the young adult life or even childhood. [7,12,20,36] The leading causes of death in CCH are the severe constrictive lung disease and the accompanying infections of the respiratory system. [27] Other causes of premature death include vascular incidents in older ages and visual disorders, due to which the possibility of serious injuries and fractures increases significantly. [4,7,14] In general, the clinical course and, therefore, the prognosis of CCH depend completely on the severity of each phenotype, the age

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of disease onset and the type of treatment intervention to be followed in each patient. [24]

12. Conclusions

CCH is an exceptionally rare inherited clinical entity that deranges bone metabolism and becomes apparent in infancy and early childhood. The disease presents with variable phenotypes of different severity and demonstrates an excessively high rate of bone turnover throughout the skeleton, resulting in the replacement of normal osseous tissue by pathological, insufficiently mineralized and reduced strength bone. That functional and histological upheaval is the reason for the serious, generalized and progressive bone deformities, the excessive increase in fracture frequency and the development of severe physical and neurological disabilities that influence in a variant negative manner life quality and expectancy of CCH patients. In the majority of cases, inactivating mutations of the TNFRSF11B gene - responsible for OPG encoding - are etiologically implicated. The diagnostic process is based on careful evaluation of clinical, laboratory and imaging data, as the combination of the various particular elements of the disease is not found in other pathological conditions. Therapeutically, current data has established BPNs as a treatment of choice, especially when administered in higher than conventional doses. However, new and more targeted treatments, such as denosumab, may further improve the clinical image and prevent the progression of the disease.

Conflict of interest:

The authors declared no conflicts of interest.

REFERENCES

1. Crespo-Peña M, Torrijos-Eslava A, Gijón-Baños J. Benign familial hyperphosphatasemia: a report of two families and review of the literature. Clin Exp Rheumatol. 1997; 15(4):425-31.
2. Thompson MD, Nezarati MM, Gillessen-Kaesbach G, et al. Hyperphosphatasia with seizures, neurologic deficit, and characteristic facial features: Five new patients with Mabry syndrome. Am J Med Genet A. 2010; 152A(7):1661-9.
3. Bakwin H, Eiger MS. Fragile bones and macrocranium. J. Pediatr. 1956; 49(5):558–64.
4. Whyte MP, Singhellakis PN, Petersen MB, et al. Juvenile Paget's disease: the second reported, oldest patient is homozygous for the TNFRSF11B "Balkan" mutation (966_969delTGACinsCTT), which elevates circulating immunoreactive osteoprotegerin levels. J Bone Miner Res. 2007; 22(6):938-46.
5. Middleton-Hardie C, Zhu Q, Cundy H, et al. Deletion of aspartate 182 in OPG causes juvenile Paget's disease by impairing both protein secretion and binding to RANKL. J Bone Miner Res. 2006; 21(3):438-45.
6. Bonakdarpour A, Maldjian C. Weiss S, et al. Hyperphosphatasemia: report of three cases. Eur J Radiol. 2000; 35(1):54-8.
7. Chong B, Hegde M, Fawkner M, et al. Idiopathic hyperphosphatasia and TNFRSF11B mutations: relationships between phenotype and genotype. J Bone Miner Res. 2003; 18(12):2095-104.
8. Silve C. Hereditary hypophosphatasia and hyperphosphatasia. Curr Opin Rheumatol. 1994; 6(3):336-9
9. Krane SM. Genetic control of bone remodeling - insights from a rare disease. N Engl J Med. 2002; 347(3):210-2.
10. Soufi M, Schoppet M, Sattler AM, et al. Osteoprotegerin gene polymorphisms in men with coronary artery disease. J Clin Endocrinol Metab. 2004; 89(8):3764–8.
11. Hagedorn C, Telgmann R, Dordelmann C, et al. Identification and functional analyses of molecular haplotypes of the human osteoprotegerin gene promoter. Arterioscler Thromb Vasc Biol. 2009 29(10): 1638-43.
12. Dunn V, Condon VR, Rallison ML. Familial hyperphosphatasemia: diagnosis in early infancy and response to human thyrocalcitonin therapy. AJR Am J Roentgenol. 1979; 132(4):541-5.
13. Whalen JP, Horwith M, Krook L, et al. Calcitonin treatment in hereditary bone dysplasia with hyperphosphatasemia: a radiographic and histologic study of bone.

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Am J Roentgenol. 1977; 129(1):29-35.
14. Antoniades K, Karakasis D, Kapetanos G, et al. Chronic idiopathic hyperphosphatasemia. Case report. Oral Surg Oral Med Oral Pathol. 1993; 76(2):200-4.
15. Stemmermann GN. An histologic and histochemical study of familial osteoectasia (Chronic idiopathic hyperphosphatasia). Am J Pathol. 1966; 48(4):641-51.
16. Cundy T, Hegde M, Naot D, et al. A mutation in the gene TNFRSF11B encoding osteoprotegerin causes an idiopathic hyperphosphatasia phenotype. Hum Mol Genet. 2002; 11(18):2119-27.
17. Cundy T, Davidson J, Rutland MD, et al. Recombinant osteoprotegerin for juvenile Paget's disease. N Engl J Med. 2005;353(9)18-23.
18. Lucas GJ, Daroszewska A, Ralston SH. Contribution of genetic factors to the pathogenesis of Paget's disease of bone and related disorders. J Bone Miner Res., 2006; 21(Suppl 2):P31-7.
19. Ralston SH. Juvenile Paget's disease, familial expansile osteolysis and other genetic osteolytic disorders. Best Pract Res Rheumatol. 2008; 22(1):101-11.
20. Whyte MP, Obrecht SE, Finnegan PM, et al. Osteoprotegerin deficiency and juvenile Paget's disease. N Engl J Med. 2002; 347(3):175-84.
21. Muntaner L, Herrera M, Saus C, et al. Hyperphosphatasemia: CT assessment. Eur Radiol. 1997; 7(1):73-6.
22. Bae KB, Kwon JH, Kim YH, et al. Juvenile Paget's disease with paranasal sinus aplasia. Clin Exp Otorhinolaryngol. 2008; 1(4):224-6.
23. Saraf SK, Gupta SK. Juvenile Paget's disease - a case report. Australas Radiol. 1989; 33(2):189-91.
24. Tau C, Mautalen C, Casco C, et al. Chronic idiopathic hyperphosphatasia: normalization of bone turnover with cyclical intravenous pamidronate therapy. Bone. 2004; 35(1):210-6.
25. Tüysüz B, Mercimek S, Ungür S, et al. Calcitonin treatment in osteoectasia with hyperphosphatasia (juvenile Paget's disease): radiographic changes after treatment. Pediatr Radiol. 1999; 29(11):838-41.
26. Sennaroğlu L, Sozeri B, Sungur A. Otological findings in idiopathic hyperphosphatasia. J Laryngol Otol. 1999; 113(2):158-60.
27. Kerr NM, Cassinelli HR, DiMeglio LA, et al. Ocular manifestations of juvenile Paget disease. Arch Ophthalmol. 2010; 128(6):698-703.
28. Klejna K, Naumnik B, Gasowska K, et al. OPG/RANK/RANKL signaling system and its significance in nephrology. Folia Histochem Cytobiol. 2009; 47(2);199-206.
29. Whyte MP. Paget's disease of bone and genetic disorders of RANKL/OPG/RANK/NF-kappaB signaling. Ann N Y Acad Sci. 2006; 1068:143-64.
30. Cundy T, Wheadon L, King A. Treatment of idiopathic hyperphosphatasia with intensive bisphosphonate therapy. J Bone Miner Res. 2004; 19(5):703-11.
31. Cassinelli HR, Mautalen CA, Heinrich JJ et al. Familial idiopathic hyperphosphatasia (FIH): response to long-term treatment with pamidronate (APD). Bone Miner. 1992;19(2):175-84.
32. Eyring EJ, Eisenberg E. Congenital hyperphosphatasia. A clinical, pathological, and biochemical study of two cases. J Bone Joint Surg Am. 1968; 50(6):1099-117.
33. McNulty JG, Pim P. Hyperphosphatasia. Report of a case with a 30 year follow-up. Am J Roentgenol Radium Ther Nucl Med. 1972; 115(3):614-8.
34. Thompson RC Jr, Gaull GE, Horwitz SJ, et al. Hereditary hyperphosphatasia. Studies of three siblings. Am J Med. 1969; 47(2):209-19.
35. Roth AJ, Abendroth K, Seidel J, et al. Management of primary idiopathic hyperphosphatasemia with calcitonin: a case report. Int Orthop. 1996; 20(1):58-60.
36. Singer F, Siris E, Shane E, et al. Hereditary hyperphosphatasia: 20 year follow-up and response to sodium etidronate. J Bone Miner Res. 1994; 9(5):733-8.
37. Simsek S, Basoski NM, Bravenboer N, et al. Sporadic hyperphosphatasia syndrome featuring periostitis and accelerated skeletal turnover without receptor activator of nuclear factor-κappaB, osteoprotegerin, or sequestosome-1 gene defects. J Clin Endocrinol Metab. 2007; 92(5):1897–901.
38. Whyte MP, Hughes AE. Expansile skeletal hyperphosphatasia is caused by a 15-base pair tandem duplication in TNFRSF11A encoding RANK and is allelic to familial expansile osteolysis." J Bone Mineral Res.2002; 17(1):26-9.
39. Whyte MP, Mills BG, Reinus WR, et al. Expansile skeletal hyperphosphatasia: a new familial metabolic bone dis-

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ease. J Bone Miner Res. 2000; 15(12):2330-44.
40. Wergedal JE, Veskovic K, Hellan M, et al. Patients with Van Buchem disease, an osteosclerotic genetic disease, have elevated bone formation markers, higher bone density and greater derived polar moment of inertia than normal. J Clin Endocrinol Metab. 2003; vol. 88(12):5778-83.
41. Crofton PM. What is the cause of benign transient hyperphosphatasemia? A study of 35 cases. Clinical Chem. 1988; 34(2):335-40.
42. Blanco O, Stivel M, Mautalen C, et al. Familial idiopathic hyperphosphatasia. A study of two young siblings treated with porcine calcitonin. J Bone Joint Surg. 1977; 59-B(4):421-7.
43. Polyzos SA, Anastasilakis AD, Terpos E, et al. Profound hypocalcemia following effective response to zoledronic acid treatment in a patient with juvenile Paget's disease. J Bone Miner Metab. 2010; 28(6):706-12.
44. Spindler, A, Berman, A, Mautalen, C, Ubios, J, Santini, EA 1992 Chronic idiopathic hyperphosphatasia: Report of a case treated with pamidronate and a review of the literature. J Rheumatol 19: 642– 645.
45. Polyzos SA, Singhellakis PN, Naot D, et al. Denosumab treatment for juvenile Paget's disease: results from two adult patients with osteoprotegerin deficiency ("Balkan" mutation in the TNFRSF11B gene). J Clin Endocrinol Metab. 2014; 99(3):703-7.
46. Grasemann C, Schundeln MM, Hovel M, et al. Effects of RANK-ligand antibody (denosumab) treatment on bone turnover markers in a girl with juvenile Paget's disease. J Clin Endocrinol Metab. 2013; 98(8):3121-6.
47. Polyzos SA, Cundy T, Mantzoros CS. Juvenile Paget disease. Metabolism. 2018; 80:15-26.
48. Cundy T, Davidson J, Rutland MD, et al. Recombinant osteoprotegerin for juvenile Paget's disease. N Engl J Med. 2005; 353(9):918-23...

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ORIGINAL PAPER

The role of skin grafts in the treatment of hand syndactyly in childhood

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ABSTRACT

Syndactyly of the hand is a frequent congenital anomaly with remarkable diversity. Medical community has been concerned about its treatment since the 19th century and many skin graft repair techniques have been proposed. There is, however, a strong reflection on their value. Between 2007 and 2016, 38 cases of hand syndactyly were treated in our clinic, in 25 children with an average age of 2.4 years. Twelve of these deformities were unilateral and 13 were bilateral. All cases were surgically repaired. Finger separation was done at the 3rd interdigital web space in 24 hands and at the 4th interdigital web space in 14 hands. In thirty-two cases syndactyly was simple and in 6 complex, while in 26 cases syndactyly was complete and in 12 incomplete. After finger separation, a free skin graft from the flexor surface of the wrist joint was used to cover the skin defects of one complex and 12 simple deformities. The abdominal area was preferred as a skin graft donor area in 14 simple and 5 complex deformity cases. In 6 cases of simple incomplete syndactyly, free skin graft repair was not required. In the follow-up which ranged from 6 months to 4 years, the results were generally considered satisfactory and all hands had excellent functionality. However, in 4 patients (15.8%), a slight extension of the newly formed interdigital web creep was noted, regardless of the graft donor area and the result was considered fair. In 4 hands (10.5%), where superficial inflammation of soft tissue developed, the end result was good. In conclusion, full thickness skin grafts are considered necessary to cover finger separation defects. The selection of the donor area is left to the surgeon's wish, as no significant correlation has been found with the final functional and cosmetic result. However, the use of a future technique where the use of skin grafts will not be required is under consideration.

Keywords: syndactyly; skin grafts; surgical plan

Introduction

Hand syndactyly is one of the most common congenital deformities. Medical community has been concerned about its treatment since the 19th century. It may appear as an individual condition or as part of a syndrome, such as those of Poland or Apert [1-4]. Syndactyly exhibits great diversity, whereas the phenotype may involve one or both of the hands, or even the lower extremities. It may also be symmetrical or asymmetric, simple, complex or complicated, com-

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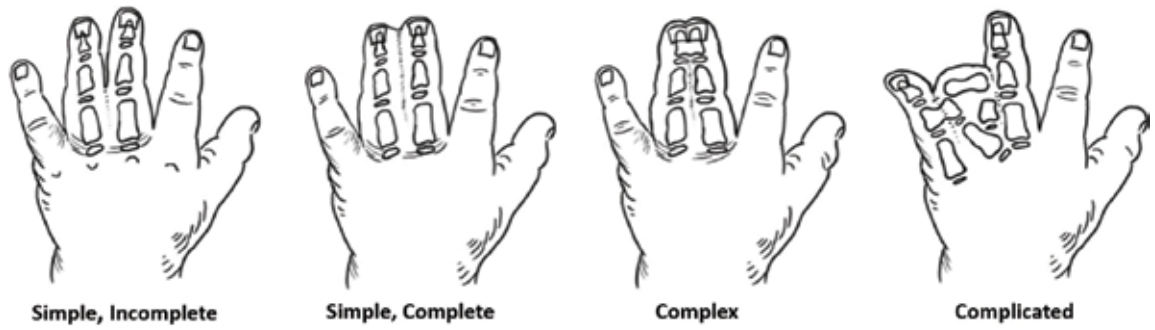

Fig. 1: *Types of hand syndactyly, depending on the size (incomplete, complete) and the participation or not of bony structures (simple, complex, complicated)*

plete or incomplete (**Figure 1**) [5, 6].

Most cases are inherited in an autosomal dominant pattern, although cases of autosomal or X-linked recessive inheritance have rarely been observed [7]. Despite the great progress in understanding the clinical and molecular identity of this deformity, little is known about its true pathogenesis [8]. Thus, the research interest in syndactyly for the coming years is obviously great.

The purpose of surgical treatment is to separate the joined fingers and ensure the skin flaps. From the early 19th century to date, there has been great progress. Since the beginning of the 20th century, the simple straight incision of the fingers with simultaneous mobilization of the local flaps was quickly replaced by the use of free skin grafts. In recent decades, using the zig-zag method and creating triangular flaps, along with wider use of grafts, many of the problems of the first period have finally found their solution [9, 10].

Creating of a sufficient size and correct shape flap for the formation of the interdigital web creep, can have a prominent role in obtaining two independent and functional fingers. This should not cause stiffness, bending or rotational deformities. Various techniques have been developed for this purpose [11]. However, for optimal cosmetic and functional results, in addition to familiarizing with the correct surgical technique, it is necessary to select the appropriate graft to cover skin defects [12].

The graft may be taken from the proximal or a remote body region, with the prospect of being directly incorporated with the skin of the recipient region, without forming shrinkage scars and impeding the functionality of the hand. The ulnar side of the wrist offers the best graft [13]. Other areas that have the potential to give an optimal full thickness graft are the femoroinguinal area [14-16], the forearm, the inner surface of the arm or the anterior surface of the thigh [14], and the foreskin in infants who are subjected to circumcision at the same time [17].

However, there is a tendency on the part of researchers to avoid using grafts, making sure to save as much skin as possible from the already existing [18-26]. Sometimes they resort to the use of an external device for soft tissue dilation before the programmed separation of the fingers [27, 28]. In cases of syndactyly that accompanies polydactyly, the excess skin from the supernumerary finger that is going to be excluded, is sufficient to cover any defect [29]. Full thickness free skin grafts are preferred, as compared to the split thickness skin grafts, as they are responsible for 7.5% of failures compared to 60% of failures respectively [30].

On the following lines, we review our ten-year clinical experience, looking for ways to better repair these deformities, especially the most difficult ones, and discuss the prospect of improving our technique.

Patients and Methods

Between January 2007 and December 2016, thirty-eight hand syndactyly cases in 25 children (14 boys and 11 girls) with an average age of 2.4 years (ranging from 9 months to 7 years) underwent surgical treatment in our department. Twelve unilateral (6 right

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Fig. 2: *A 1-year-old female infant with a simple-incomplete syndactyly at the 3rd in-terdigital web space of the left hand (patient 8).*

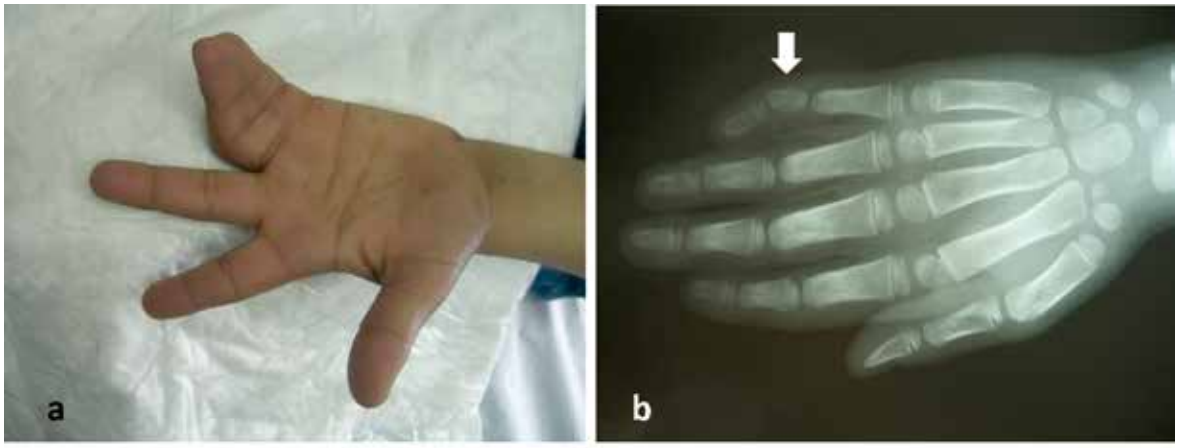

Fig. 3*: A 2.5-year-old male toddler with a simple-complete syndactyly at the 4th inter-digital web space of the left hand (patient 19). a) Preoperative clinical picture b) A hand x-ray where the presence of a deltoid middle phalange of the small finger is indicated (arrow).*

and 6 left hands) and 13 bilateral deformities were repaired. Finger separation was done at the 3rd interdigital web space in 24 hands (**Figure 2**) and at the 4th interdigital web space in 14 hands (**Figure 3**). From our study were excluded children who suffered from Apert syndrome and syndactyly cases in patients with polydactyly. Thirty-two deformities were simple and 6 complex. Twenty-six of them were complete and 12 incomplete (**Table 1**). After finger separation, a free skin graft from the flexor surface of the wrist joint was used to cover the skin defects of one complex and 12 simple deformities (13 complete syndactyly cases). The abdominal area was preferred as a skin graft donor area in the case of 14 simple and 5 complex deformities (13 complete and 6 incomplete syndactyly cases). In 6 cases of simple incomplete syndactyly, free skin graft repair was not required.

Surgical technique

Under general anesthesia and the application of a pneumatic tourniquet, the hand is properly cleaned with an antiseptic solution and the skin incisions are designed, both on the dorsal and palmar surface. Reservation of sufficient dorsal skin flap is of great impor-

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No	Age/Sex	Donor site	Simple Complex	Incomplete Complete	Web space	Follow-up period	Complications	Results
1	5 years/M	Abdomen	Simple	Incomplete	Bilateral/3rd	6 months	Nil	Good
2	1 year/F	Wrist	Simple	Complete	Left/3rd	24 months	Web creep	Fair
3	0.9 years/F	Wrist	Simple	Complete	Right/3rd	36 months	Nil	Good
4	6 years/M	Abdomen	Simple	Incomplete	Bilateral/3rd	6 months	Nil	Good
5	2 years/M	Wrist	Complex	Complete	Right/3rd	48 months	Nil	Good
6	4 years/M	Abdomen	Simple	Complete	Left/3rd	36 months	Nil	Good
7	1.5 years/F	Abdomen	Simple	Complete	Right/3rd	24 months	Web creep	Fair
8	1 year/F	Abdomen	Simple	Incomplete	Bilateral/3rd	6 months	Nil	Good
9	1.5 years/M	Wrist	Simple	Complete	Left/4th	48 months	Infection	Good
10	2.5 years/M	Abdomen	Complex	Complete	Bilateral/4th	12 months	Nil	Good
11	1 year/F	Wrist	Simple	Complete	Right/3rd	36 months	Nil	Good
12	0.9 years/F	No graft	Simple	Incomplete	Bilateral/4th	24 months	Web creep	Fair
13	7 years/M	Abdomen	Simple	Complete	Bilateral/3rd	9 months	Nil	Good
14	1 year/F	Wrist	Simple	Complete	Bilateral/3rd	48 months	Infection	Good
15	1 year/F	No graft	Simple	Incomplete	Bilateral/4th	12 months	Nil	Good
16	1.5 years/F	Wrist	Simple	Complete	Left/4th	6 months	Nil	Good
17	2 years/M	Abdomen	Simple	Complete	Bilateral/4th	48 months	Nil	Good
18	3 years/M	Abdomen	Complex	Complete	Bilateral/3rd	48 months	Nil	Good
19	2.5 years/M	Wrist	Simple	Complete	Bilateral/4th	9 months	Nil	Good
20	1.5 years/F	No graft	Simple	Incomplete	Left/3rd	48 months	Nil	Good
21	1 year/F	Wrist	Simple	Complete	Bilateral/3rd	6 months	Nil	Good
22	4.5 years/M	Abdomen	Complex	Complete	Left/3rd	24 months	Nil	Good
23	2 years/M	Abdomen	Simple	Complete	Bilateral/3rd	12 months	Web creep	Fair
24	1.5 years/M	Wrist	Simple	Complete	Right/4th	48 months	Nil	Good
25	3.5 years/M	No graft	Simple	Incomplete	Right/4th	9 months	Infection	Good

Table 1 *Patients' data of the study*

tance in creating the interdigital web creep. Zig-zag incisions are used in order to form triangular flaps and cover the adjacent surfaces of separated fingers (**Figure 4**). During finger separation, great care is also taken to ensure the integrity of the neurovascular bundles. Magnifying surgical loupes are required for this reason. In complex deformity cases, thin metal osteotomes are used to separate the bones.

In order to obtain full thickness skin grafts and cover the skin deficits before surgery begins, we select as donor area either the flexor surface of the wrist joint or the abdominal area over the femoroinguinal crease. Skin incision is spindle-shaped and during grafting we take care to remove subcutaneous fat (**Figure 5**). We also recommend making the graft discontinuous, with thin parallel incisions, made with a No.15 scalpel blade. Suturing of skin flaps and grafts in the recipient regions is performed according to the principles of Plastic Surgery using non-absorbable sutures, preferably 4-0 or 5-0 nylon (**Figure 6**). We do the same for repairing the donor area.

Bleeding is checked, the pneumatic tourniquet is removed and the hand is covered with gauze dressings. Then it is immobilized using cotton and elastic band-

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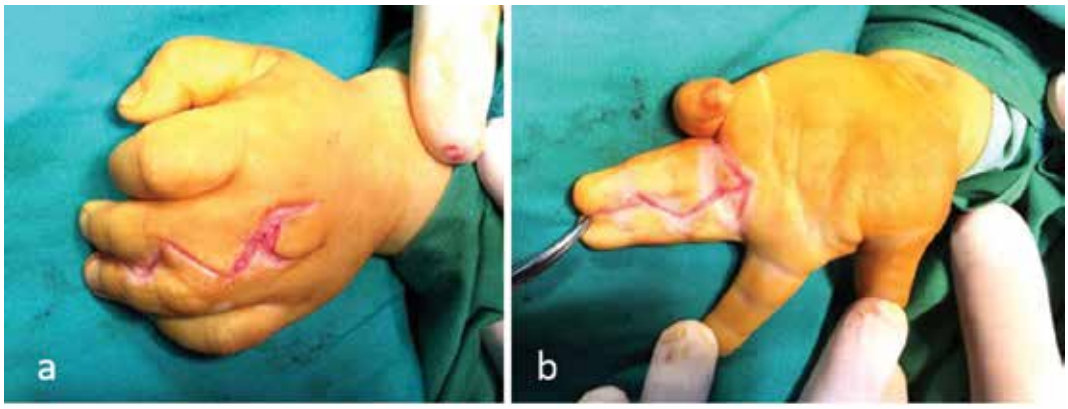

***Fig. 4**: Creation of triangular flaps using zig-zag incisions a) on the dorsal surface and b) the palmar surface.*

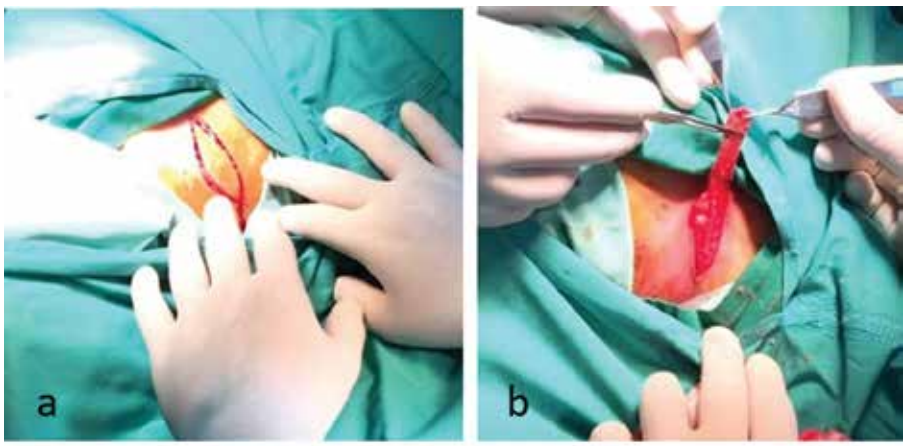

***Fig. 5**: A full-thickness skin graft from the abdominal area over the femoroinguinal crease. a) A spindle-shaped skin incision b) Removal of the subcutaneous fat from the graft before it is separated from the donor area.*

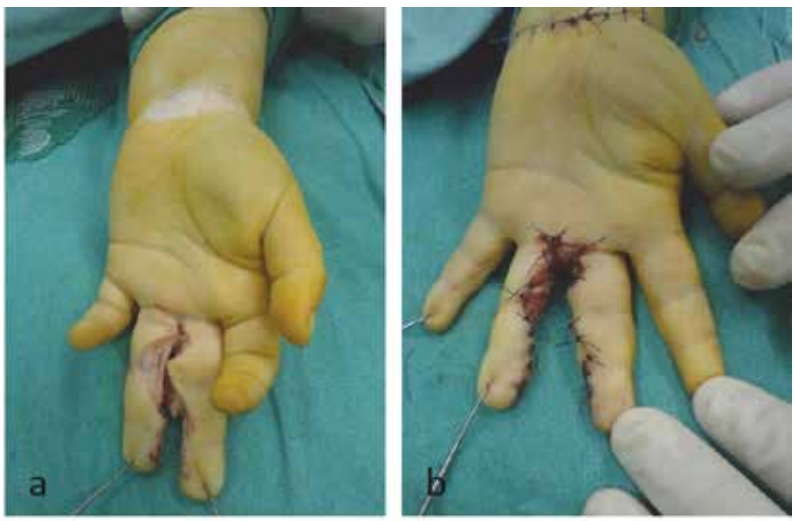

***Fig. 6:** Middle finger-ring finger separation in a patient with a simple-complete syndactyly of the left hand (patient 21). a) Triangular flaps and taking of full-thickness graft from the flexor surface of the wrist joint b) Suturing of the triangular flaps and grafts for covering skin deficits according to the principles of Plastic Surgery.*

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	Pigmentation
0	Close to normal
1	Hypopigmented
2	Mixed
3	Hyperpigmented
	Pliability
0	Close to normal
1	Supple
2	Yielding
3	Firm
4	Banding
5	Contracture
	Height
0	Flat
1	<2 mm
2	2-5 mm
3	>5 mm
	Vascularity
0	Normal
1	Pink
2	Red
3	Purple

Table 2 *Vancouver Scar Scale*

ages in the shape of a boxing glove. Wound dressings are changed after 7 and 10 days, while the sutures are removed after 2 weeks. Complete return of the patient to normal activities is allowed after 4 weeks.

Fig. 7: *Grading of the length of a newly formed interdigital web creep according to the Withey grading system (2001) on the left hand of the patient 21, six months after finger separation. On the basis of the above system's criteria, the result was excellent.*

0	Soft web, abduction mirrors the adjacent web or equivalent web on the other hand
1	Thickening of the web without advancement
2	1/3 web creep recurrence of distance from palmar MCP to PIP joint crease
3	2/3 web creep recurrence of distance from palmar MCP to PIP joint crease
4	Web creep recurrence of the full extent from the palmar MCP crease to PIP joint crease

Table 3 *Grading of web creep modified according to Withey et al (2001)*

Results

During patient follow-up which ranged from 6 months to 4 years, the results were generally considered satisfactory. According to the clinical criteria of the Vancouver Scar Scale (**Table 2**), which takes into account the possibility of skin pigmentation, the pres-

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ervation of its elasticity, the length of the interdigital web creep and the vascularity of the separated fingers, no serious changes were found.

According to the Withey modified grading system, regarding the size of the newly formed interdigital web creep, four patients were found to have a small degree of elongation (**Figure 7, Table 3**). One of them was a 12-month-old female infant with a simple-complete syndactyly at the third interdigital web space of left hand. Another patient was an 18-month-old female infant with a simple-complete syndactyly at the third interdigital web space of right hand. A third patient case was about a 9-month-old female infant with a simple-incomplete syndactyly at the fourth interdigital web space of both hands. In the first case, a free skin graft from the area of the wrist joint was used, in the second case the donor area was the abdomen, while in the third case no skin grafts were needed. Finally in a 2-year-old boy with a simple-complete syndactyly of his both hands at the third interdigital web space, where a skin graft from the abdominal area was used, a slight interdigital web creep elongation was also observed. In all these cases (15.8%), the results were found to be fair.

Four hands (10.5%) developed superficial soft tissue inflammation and were successfully treated with frequent wound changes and antibiotics. In these cases, the end result was considered good.

Discussion

Our study did not include syndactyly cases accompanied by polydactyly due to the need to compare similar deformities. We also did not include cases belonging to syndromes (Apert or Poland) because they were few in number and could not be statistically evaluated. In this study were included cases of incomplete or complete, simple or complex syndactyly. Patients with complicated syndactyly were transferred to a special center where they could be treated by a medical team of Plastic Surgery.

The average age of our patients was 2.4 years, while all of them were older than 9 months old. For the reconstruction of simple syndactyly, patients aged over 6 months old are preferred, although many authors prefer ages over 18 months old [31]. We believe that choosing the right timing is of vital importance because it prejudges the good result. In Greek reality, it is common for parents to put pressure on doctors for early reconstruction of the deformity, if possible in the first few weeks after birth. Such cases must be handled wisely.

We have established our technique for the past 15 years and we are very satisfied with the results. However, we would gladly accept any new technique that could facilitate finger separation or avoid the use of skin grafts. We consider the careful removal of fat from the graft as important as its discontinuous modification with thin parallel incisions. We prefer the use of nylon sutures because they are monofilament and leave smaller scars, although general anesthesia is often required in order to be removed. After completion of skin suturing, we release the tourniquet band. If we detect poor blood flow, we cut the sutures that are considered responsible. In cases of synonychia, we proceed to a detailed separation of the distal phalanges, making sure to cover the created skin deficit by graft, according to the literature guidelines [32].

In order to select a full thickness skin graft instead of a split thickness, we did not have the slightest hesitation, as we are convinced that the chances of failure of the technique are more with the second option [30]. A split thickness skin graft was not used in any of the study patients. Regarding the color of graft, we did not notice any problems, although grafts from the ulnar surface of the wrist are considered the safest [33].

The goals of the proper management of syndactyly are: a) to create an interdigital web creep without shrinking, bending or rotational deformities of the separated fingers and b) to cover skin deficits with the appropriate grafts. Some authors consider the second goal to be of prime importance [34]. However, complications of inability to achieve the first goal are not uncommon [35].

In childhood syndactyly cases, techniques that give excellent results to adults, such as the use of bilobed flaps from the dorsal surface, as described by Sahin et al. [36], have not yet been used. However, we must bear in mind that the right choice of the donor area may limit the possibility of other complications. The inguinal region is selected to refer to a region away

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from the mons pubis in order to avoid unacceptable hair growth [14]. The inner surface of the arm has been almost abandoned because it is implicated in the formation of an ugly scar in the donor area. In the literature, there are many articles suggesting different donor areas for skin grafts [13,33] and others with areas to be avoided [37-39]. In an attempt to replace flaps with the V-Y technique that is quite popular in finger separation [21,40], Aydin and Ozden [18] suggest a pedicle vascular flap to create a secure interdigital web creep.

The short patient follow-up (6 months to 4 years) is perhaps the weak point of our work, but we intend to reassess these cases along with the registration of new patients after a reasonable period of time. Dao et al. suggest that patients should be screened on a regular basis until completion of skeletal maturation in order to prevent or treat any further complications [31].

Conclusion

Syndactyly can be combined with other complex abnormalities that affect the end result. Careful preoperative study is required with regard to indications, correct timing, flap design, and donor area selection for skin graft use. Orthopedic surgeon must be fully aware of the anatomical structure and the various and varied variants.

Conflict of interest:

The authors declared no conflicts of interest.

REFERENCES

1. Wilson MR, Louis DS, Stevenson TR. Poland's syndrome: variable expression and associated anomalies. J Hand Surg Am 1988; 13: 880.
2. Eaton CJ, Lister GD. Syndactyly. Hand Clin 1990; 6(4): 555-575.
3. Zucker RM, Cleland HJ, Haswell T. Syndactyly correction of the hand in Apert syndrome. Clin Plast Surg 1991; 18(2): 357-364.
4. Visser JD. Pediatric Orthopedics: symptoms, differential diagnosis, supplementary assessments and treatment. Springer International Publishing, 2017, pp 99-116.
5. Jobe MT. Congenital anomalies of hand. In S. Terry Canale's (ed): Campbell's Operative Orthopaedics, 10th edition, 2003, pp 3827-3905, Mosby.
6. Malik S, Grzeschik KH. Synpolydactyly: clinical and molecular advances. Clin Genet 2008; 73(2): 113-120.
7. Malik S. Syndactyly: phenotypes, genetics and current classification Eur J Hum Genet 2012; 20(8): 817-824.
8. Jordan D, Hindocha S, et al. The epidemiology, genetics and future management of syndactyly. Open Orthop J 2012; 6: 14-27.
9. Cronin TD. Syndactylism: results of zig-zag incision to prevent postoperative contraction. Plast Reconstr Surg 1956; 18: 460.
10. van der Biezen JJ, Bloem JJ. Dividing the fingers in congenital syndactyly release: a review of more than 200 years of surgical treatment. Ann Plast Surg 1994; 33(2): 225-230.
11. Miyamoto J, Nagasao T, Miyamoto S. Biomechanical analysis of surgical correction of syndactyly. Plast Reconstr Surg 2010; 125(3): 963-968.
12. Vekris MD, Lykissas MG, et al. Congenital syndactyly: outcome of surgical treatment in 131 webs. Tech Hand Up Extrem Surg 2010; 14(1): 2-7.
13. Park S, Hata Y, et al. Full-thickness skin graft from the ulnar aspect of the wrist to cover defects on the hand and digits. Ann Plast Surg 1999; 42(2): 129-131.
14. Deunk J, Nicolai JPA, Hamburg SM. Long-term results of syndactyly correction: Full-thickness versus split thickness skin grafts. J Hand Surg Br 2003; 28(2): 125-130.
15. Lumenta DB, et al. Long-term outcomes of web creep, scar quality, and function after simple syndactyly surgical treatment. J Hand Surg 2010; 35A: 1323-1329.
16. Barabás AG, Pickford MA. Results of syndactyly release using a modification of the Flatt technique. J Hand Surg Eur 2014; 39(9): 984-988.

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17. Oates SD, Gosain AK. Syndactyly repair performed simultaneously with circumcision: use of foreskin as a skin-graft donor site. J Pediatr Surg 1997; 32(10): 1482-1484.
18. Aydin A, Ozden BC. Dorsal metacarpal island flap in syndactyly treatment. Ann Plast Surg 2004; 52(1): 43-48.
19. Niranjan NS, et al. Long-term results of primary syndactyly correction by the trilobed flap technique. Br Assoc Plast Surg 2005; 58: 14-21.
20. Tan O, Atik B, Ergen D. Versatile use of the VM-plasty for reconstruction of the web space. Ann Plast Surg 2005; 55(6): 623-628.
21. Hsu VM, Smartt Jr JM, Chang B. The modified V-Y dorsal metacarpal flap for repair of syndactyly without skin graft. Plast Reconstr Surg 2010; 125:225-232.
22. Gao W, et al. Dorsal pentagonal local flap: A new technique of web reconstruction for syndactyly without skin graft. Aesth Plast Surg 2011; 35: 530-537.
23. Matsumine H, et al. Improved "bell-bottom" flap surgical technique for syndactyly without graft. Plast Reconstr Surg 2011; 128: 504e-509e.
24. Liu J, et al. Dorsal plane-shaped advancement flap for the reconstruction of web space in syndactyly without skin grafting: A preliminary report. J Plast Reconstr Aesth Surg 2015; 68: e167-e173.
25. Ni F, et al. The use of an hourglass dorsal advancement flap without skin graft for congenital syndactyly. J Hand Surg Am 2015; 40(9): 1748-1754.
26. Dong Y, Wang Y. The use of a dorsal double-wing flap without skin grafts for congenital syndactyly treatment. Medicine 2017; 96:1-6.
27. Vladimir I, et al. Application of external fixation for management of hand syndactyly. Int Orthop 2008; 32(4): 535-539.
28. Kvemmo HD, Haugstvedt JR. Treatment of congenital syndactyly of the fingers. Tidsskr Nor Laegeforen 2013; 133(15): 1591-1595.
29. Rowsell AR, Godfrey AM. A fortuitous donor site for full-thickness skin grafts in the correction of syndactyly. Br J Plast Surg 1984; 37(1): 31-34.
30. Deutinger M, Mandl H, et al. Late results following surgical correction of syndactyly and symbrachydactyly. Z Kinderchir 1989; 44(1): 50-54.
31. Dao KD, Shin AY, Billings A, et al. Surgical treatment of congenital syndactyly of the hand. J Am Acad Orthop Surg 2004; 12(1): 39-48.
32. Sommerkamp TG, Ezaki M, et al. The pulp plasty: a composite graft for complete syndactyly fingertip separations. J Hand Surg Am 1992; 17(1): 15-20.
33. Zoltie N, Verlende P, Logan A. Full-thickness grafts taken from the plantar instep for syndactyly release. J Hand Surg Br 1989; 14(2): 201-203.
34. Percival NJ, Sykes PJ. Syndactyly: a review of the factors which influence surgical treatment. J Hand Surg Br 1989; 14(2): 196-200.
35. Tonkin MA, Willis KR, Lawson RD. Keloid formation resulting in acquired syndactyly of an initially normal web space following syndactyly release of an adjacent web space. J Hand Surg Eur Vol 2008; 33(1): 29-31.
36. Sahin C, et al. Bilobed flap for web reconstruction in adult syndactyly release: A new technique that can avoid the use of skin graft. J Plast Reconstr Aesth Surg 2014; 67: 815-821.
37. Ekerot L. Syndactyly correction without skin-grafting. Journal of Hand Surgery 1996; 21B: 330–337.
38. Greuse M, Coessens BC. Congenital syndactyly: defatting facilitates closure without skin graft. Journal of Hand Surgery 2001; 26A: 589–594.
39. Withey SJ, et al. The open finger technique for the release of syndactyly. J Hand Surg 2001; 26B: 4 –7.
40. Sherif MM. V-Y dorsal metacarpal flap: a new technique for the correction of syndactyly without skin graft. Plast Reconstr Surg 1998; 101(7): 1861-1866.

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MINI REVIEW

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The importance of bearing surfaces in hip replacement

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ABSTRACT

Hip replacement is a successful operation. The increase of life expectancy increased also the number of patients with hip arthritis. It also highlighted the need to produce implants that would last longer. This mini review article provides information about the important role of bearing surfaces in the longevity of hip replacements as well as their evolution over time.

Keywords: hip replacement; bearings; longevity; ceramics; polyethylene; vitamin E

Introduction

More than a century has passed since 1891, when Dr Themistocles Glück performed the first total hip replacement [1]. Innovation and research generated by the growing need of arthritic patients to maintain a good quality of life, led to the introduction of the first modern, low friction, total hip replacement by Sir John Charnley [2]. His pioneering work laid the foundation to an industry expected to be worth 9.1 billion dollars by 2024 [3]. Numerous types of fixations, various prosthesis shapes and different bearing surfaces have been introduced since then. Their overall results were good enough to make total hip replacement one of the most popular and successful operations in orthopaedic surgery.

However, apart from good functional outcome and pain alleviation, component survival has also been a concern. The increase in life expectancy increased also the number of people suffering from arthritis. In addition, it highlighted the need for implants that would last long enough and prevent younger patients from having revision surgery.

Numerous studies demonstrated that the survival of hip arthroplasty implants was inversely proportional to the size and number of static and dynamic loads they bear. Longevity could therefore vary according to patient body weight, age and lifestyle [4,5,6]. Moreover, implant wear is related to the material and size of the load bearing surfaces [7,8].

Aseptic loosening is the primary cause for hip revision. This devastating complication is resulting from a particle disease caused by femoral head movement on

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the acetabular liner [9]. Tribology was used to investigate the reasons causing osteolysis. The latter is the science that studies the behavior of various materials that are in relative motion. It is considered fundamental for the study of prostheses survival and the development of new bearings.

The bearing surfaces used in modern hip replacements are either ceramic on ceramic (CoC), metal on polyethylene (MoP) or ceramic on polyethylene (CoP).

CoC bearings exhibit increased hardness and scratch resistance. These features warrant optimal lubrication thus lowering friction and consequently preventing debris accumulation. Furthermore, CoC allow the use of larger femoral heads irrespective of the thickness of the acetabular liner. Thus, greater femoral head-neck ratio and increased jump distance are achieved that offer better range of motion and improved stability [10]. Hernigou et al found an additional reason for CoC's lower dislocation rate. He observed that the capsule in COC bearings was thicker, thus providing greater stability than the elastic tissue seen when polyethylene cups are used. He therefore attributed the lower dislocation rate to a different joint capsule histology. [11].

The major weaknesses of CoC bearings are their brittleness, high cost and the production of annoying squeaking sounds. Brittleness of alumina ceramics was a big concern when CoC were first used. That issue was addressed with the introduction of strontium oxide platelets and zirconium particles. Consequently, the incidence of fractures dropped significantly from 0.021% to 0.003% [12]. However, their relatively high cost and squeaking sound issues have yet to be addressed.

MoP was first introduced by Sir John Charnley in 1961. Ultra high molecular weight polyethylene (UHMWPE) is a material with chemical inertness, low antigenicity and low friction coefficient. These advantages made it the most popular bearing in hip arthroplasty. However, despite the good post-operative outcome, the wear rate of UHMWPE was considerably high. The articulation between the metal head and UHMWPE produced significant amount of wear particles that induced an inflammatory response. Consequently, osteolysis and loosening occured that ultimately increased the need for revision surgery.

The development of highly cross-linked polyethylene (XLPE) offered solutions to the problems caused by UHMWPE and played an important role in retaining the popularity of MoP [13,14,15]. XLPE is the outcome of a process responsible for altering the molecular structure of polyethylene, thus making it more durable to adhesive and abrasive wear. Some studies even suggested that it decreased wear in vitro by 92%[16]. These properties instigated a remarkable decrease of linear penetration and volumetric wear, even though the former is also affected by the size of the femoral head. The incidence of osteolysis and implant loosening decreased by 69.4% at 15 years after primary hip replacement [14]. Moreover, XPLE decreased the revision rates of MoP to an extent that they are now comparable with other modern bearings [13].

MoP continue to be the most commonly used bearings in hip arthroplasty, however they are not anymore the most common in young patients. Next generation XLPE may have offered peace of mind to arthroplasty surgeons, however CoC exhibit lower rates for revision, osteolysis, aseptic loosening and dislocation [17,18,19,20]. The superiority of CoC is indisputable but the issues of squeaking and brittleness are still preventing surgeons from using it. In fact, over the last 7 years arthroplasty surgeons exhibit a steadily increasing preference for CoP bearings, especially in younger patients [13].

CoP bearings combine the properties of ceramics and next generation XLPE. They are hard-on-soft bearings linked with considerably lower fracture risk than CoC. Furthermore, they have not been linked yet with squeaking sounds [21]. CoP have similar Harris hip scores, loosening rates and dislocation rates with CoC [22]. However, due to volumetric polyethylene wear being dependent to the size of femoral heads, ceramic heads larger than 36mm are not recommended [13]. Moreover, they have higher survival rate than MoP and CoC, even though their wear rate is higher than CoC [23].

Second generation highly cross-linked polyethylene use vitamin E as an antioxidant to further reduce polyethylene oxidization. Since they have been in the market for less than 10 years, only a small number of

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studies have investigated the survival of these components. Apart from preventing polyethylene oxidization, vitamin E diffusion is believed to improve fatigue strength, reduce the biological activity of wear debris and lower the risk for infection [24]. A recent study about the 5-year in vivo experience with vitamin E diffused XLPE, showed that the latter demonstrated lower head penetration compared to non-vitamin E diffused liners [25]. Moreover, other studies demonstrated that second generation XPLE were superior to older polyethylene liners in restraining damage caused after neck and liner impingement [26].

Discussion

MoP remains the most used bearing in hip arthroplasty. But this is because the majority of people having hip replacement are over 70. In young patients there is an evident preference towards using ceramic bearing surfaces. Since their issues with brittleness and squeaking haven't been solved there was a need for a third option. The production of XLPE made CoP bearings a good option for young people that need implants with greater longevity.

Conclusion

Even though the information coming for vitamin E diffused polyethylene is promising, more time is needed to understand if the perfect polyethylene has been created. However, it is safe to say that with the application of new materials and the gradual drop of revision rates we are on the right track for making hip replacement an even more successful operation.

Conflict of interest:

The authors declared no conflicts of interest.

Abbreviations: ceramic on ceramic (CoC),
metal on polyethylene (MoP),
ceramic on polyethylene (CoP),
ultra high molecular weight polyethylene (UHMWPE),
highly cross-linked polyethylene (XLPE)

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REFERENCES

1. Eynon-Lewis NJ, Ferry D, Pearse MF. Themistocles Gluck: an unrecognised genius. BMJ. 1992 Dec 19-26;305(6868):1534-6. PubMed PMID: 1286374; PubMed Central PMCID: PMC1884727.
2. Gomez PF, Morcuende JA. A historical and economic perspective on Sir John Charnley, Chas F. Thackray Limited, and the early arthoplasty industry. Iowa Orthop J. 2005;25:30-7.
3. No Author. Hip Replacement Implants Market By Product Type Analysis (Total Replacement Implant, Partial Replacement Implant, Hip resurfacing Implant, Revision Replacement Implant); By Materials Analysis (Metal-on-metal, Metal-on-polyethylene, Ceramic-on-metal, Ceramic-on-polyethylene, Ceramic-on-ceramic) By End Users Analysis (Hospitals, Orthopedic Clinics, Ambulatory Surgical Centers) and By Regional Analysis – Global Forecast by 2018 – 2024
4. Barrett M, Prasad A, Boyce L, et al. Total hip arthroplasty outcomes in morbidly obese patients: A systematic review. EFORT Open Rev. 2018;3(9):507-512. Published 2018 Sep 24. doi:10.1302/2058-5241.3.180011
5. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Meyer HE. The effect of middle-age body weight and physical activity on the risk of early revision hip arthroplasty: a cohort study of 1,535 individuals. Acta Orthop. 2007 Feb;78(1):99-107. PubMed PMID: 17453400.
6. Prokopetz JJZ , Losina E , Bliss RL et al. Risk factors for revision of primary total hip arthroplasty: a systematic review. BMC Musculoskeletal Disorders 2012;13:251:
7. Tsikandylakis G, Mohaddes M, Cnudde P, Eskelinen A, Kärrholm J et al. Head size in primary total hip arthroplasty. EFORT Open Rev. 2018;3(5):225-231. Published 2018 May 21. doi:10.1302/2058-5241.3.170061
8. Rieker CB. Tribology of total hip arthroplasty prostheses: What an orthopaedic surgeon should know. EFORT Open Rev. 2016;1(2):52-57. Published 2016 Feb 29. doi:10.1302/2058-5241.1.000004
9. Willert HG, Semlitsch M. Reactions of the articular capsule to wear products of artificial joint prostheses. J Biomed Mater Res. 1977 Mar;11(2):157-64. PubMed PMID: 140168.
10. Cho MR, Choi WK, Kim JJ. Current Concepts of Using Large Femoral Heads in Total Hip Arthroplasty. Hip Pelvis. 2016;28(3):134-141.
11. Hernigou P, Homma Y, Pidet O, Guissou I, Hernigou J. Ceramic-on-ceramic bearing decreases the cumulative long-term risk of dislocation. Clin Orthop Relat Res. 2013;471(12):3875-82.
12. Massin P, Lopes R, Masson B, Mainard D; French Hip & Knee Society (SFHG). Does Biolox Delta ceramic reduce the rate of component fractures in total hip replacement? Orthop Traumatol Surg Res. 2014 Oct;100(6 Suppl):S317-21. doi: 10.1016/j.otsr.2014.05.010. Epub 2014 Aug 12. Review. PubMed PMID: 25130763.
13. No Author. National joint registry for England, Wales, Northern Ireland and the Isle of Man. 2017 Annual Report. http://www.njrcentre.org.uk/njrcentre/ Reports,PublicationsandMinutes/Annualreports/tabid/86/Default.aspx(date last accessed 7 March 2018).
14. No Author. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR): 2017 Annual Report. https://aoanjrr.sahmri.com/annual-reports-2017 (date last accessed 7 March 2018).
15. No Author. Swedish Hip Arthroplasty Register Annual Report 2014. https://registercentrum.blob.core.windows.net/shpr/r/Annual-report-2014-BJv-q8pil.pdf (date last accessed 7 March 2018).
16. Liao YS , Greer K , Hanes M et al. Effects of Resin and Dose on Wear and Mechanical Properties of Cross-Linked Thermally Stabilized UHMWPE. Society for Biomaterials, the 7th World Biomaterials Congress: Sydney, NSW, Australia, 2004.
17. Vendittoli P, Girard J, Lavigne M, Lavoie P, Duval N. Comparison of alumina-alumina to metal-polyethylene bearing surfaces in THA: a randomized study with 4- to 9-years follow-up. Acta Orthop Belg. 2007 Aug;73(4):468-77. PubMed PMID: 17939477.
18. Bascarevic Z, Vukasinovic Z, Slavkovic N, Dulic B, Trajkovic G et al. Alumina-on-alumina ceramic versus metal-on-highly cross-linked polyethylene bearings in total hip arthroplasty: a comparative study. Int Orthop. 2010 Dec;34(8):1129-35. doi:

VOLUME 70 | ISSUE 2 | APRIL - JUNE 2019

10.1007/s00264-009-0899-6. Epub 2009 Nov 1. PubMed PMID: 19882338; PubMed Central PMCID: PMC2989085.

19. D'Antonio JA, Capello WN, Naughton M. Ceramic bearings for total hip arthroplasty have high survivorship at 10 years. Clin Orthop Relat Res. 2012 Feb;470(2):373-81. doi: 10.1007/s11999-011-2076-7. PubMed PMID: 21918802; PubMed Central PMCID: PMC3254761.
20. Nikolaou VS, Edwards MR, Bogoch E, Schemitsch EH, Waddell JP. A prospective randomised controlled trial comparing three alternative bearing surfaces in primary total hip replacement. J Bone Joint Surg Br. 2012 Apr;94(4):459-65. doi: 10.1302/0301-620X.94B4.27735. PubMed PMID: 22434459.
21. Amanatullah DF, Landa J, Strauss EJ, Garino JP, Kim SH et al. Comparison of surgical outcomes and implant wear between ceramic-ceramic and ceramic-polyethylene articulations in total hip arthroplasty. J Arthroplasty. 2011 Sep;26(6 Suppl):72-7. doi: 10.1016/j.arth.2011.04.032. Epub 2011 Jun 15. PubMed PMID: 21680138.
22. Parsons C, Batson R, Reighard S, Tanner S, Snider B et al. Clinical outcomes assessment of three similar hip arthroplasty bearing surfaces. Orthop Rev (Pavia). 2014;6(2):5334. Published 2014 May 22. doi:10.4081/or.2014.5334
23. Meftah M, Klingenstein GG, Yun RJ, Ranawat AS, Ranawat CS. Long-term performance of ceramic and metal femoral heads on conventional polyethylene in young and active patients: a matched-pair analysis. J Bone Joint Surg Am. 2013 Jul 3;95(13):1193-7. doi: 10.2106/JBJS.L.00432. PubMed PMID: 23824387.
24. Yamamoto K, Tateiwa T, Takahashi Y. Vitamin E-stabilized highly crosslinked polyethylenes: The role and effectiveness in total hip arthroplasty. J Orthop Sci. 2017 May; 22(3):384-390. doi: 10.1016/j.jos.2017.01.012. Epub 2017 Feb 11. PubMed PMID: 28209339.
25. Nebergall, Audrey K. et al. Five-Year Experience of Vitamin E–Diffused Highly Cross-Linked Polyethylene Wear in Total Hip Arthroplasty Assessed by Radiostereometric Analysis. The Journal of Arthroplasty, Volume 31, Issue 6 , 1251 - 1255
26. Takahashi Y, Tateiwa T, Pezzotti G, Shishido T, Masaoka T et al. Improved Resistance to Neck-Liner Impingement in Second-Generation Highly Crosslinked Polyethylene-The Role of Vitamin E and Crosslinks. J Arthroplasty. 2016 Dec;31(12):2926-2932. doi: 10.1016/j.arth.2016.05.049. Epub 2016 Jun 1. PubMed PMID: 27378642.

READY - MADE CITATION

Economopoulos D., Vlamis I., Chronopoulos E., Triantafyllopoulos I.K. The importance of bearing surfaces in hip replacement. *Acta Orthop Trauma Hell* 2019; 70(2): 52-56.

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MINI REVIEW

Spinal deformity in children

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ABSTRACT

The treatment of early onset scoliosis is a challenge because of the need to correct the deformity of the spine without using the traditional systems that require spinal fusion at this age. The conservative treatment of early onset scoliosis with brace is usually not effective but can help to postpone the surgical treatment at a time closer to skeletal maturation. The surgical procedure includes systems that do not fuse the spine but allow for further growth. These systems can be (a) the growing rods, (b) the guided rods and (c) compressive-based. These systems are a good option for the treatment of childhood scoliosis, but as they are not «protected» by a bone spine fusion they are subject to ongoing stress and forces. As a result, there is a higher failure rate of materials compared to the traditional fusion systems.

KEY WORDS: early onset scoliosis; thoracic insufficiency syndrome; growing brace for scoliosis; growing rods; guided rods; compressive-based system

Introduction

Scoliosis is a three-dimensional deformity of the spine in which there is a shift of the vertebrae, and abnormal curves that are mainly at the side of the spine. This deformity can be observed in children before puberty. In some cases, the scoliosis is progressive, and the deformation of the rib cage can affect the development of pulmonary alveoli. During this period there is a need to protect the rib cage from deformation and lessen the effects on the pulmonary parenchyma. On the other hand, we can't correct the deformity with spinal fusion and suspend its development because that will limit the growth of the rib cage, causing obstructive pulmonary disease. The inability to interfere in scoliosis developed in young children can lead to serious scoliosis with serious co-morbid obstructive pulmonary disease. For all the above reasons these deformities are a distinct clinical entity termed «early onset" scoliosis and appears before the age of 10[1]. The way the scoliosis is going to develop depends on the etiology (congenital, neuromuscular, syndromic, i.e. neurofibromatosis, and idiopathic). Some syndromic scoliosis with congenital anomalies such as asphyxiating thoracic dysplasia (Jeune's Syndrome) and the vertebra-rib dysostosis (Jarcho-Levin-Syndrome) will take a very special and demanding treatment.

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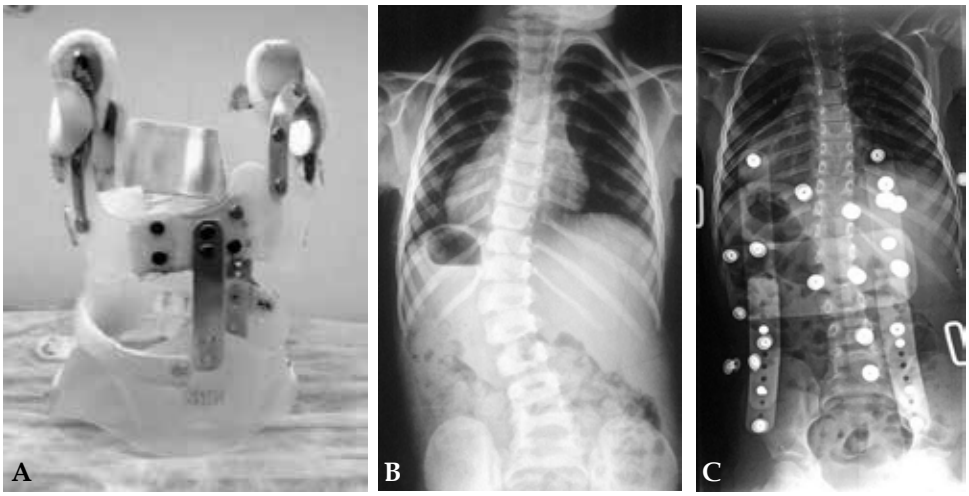

Figure 1. *Treatment with a growing brace (A). The initial scoliosis of a girl of 1 years old with left thoracolumbar curve was 33° (B) and after 1 year of bracing that improved at 12° (C).*

Thoracic insufficiency syndrome

The goal of the treatment of early scoliosis is to stop the deterioration of scoliosis into severe deformation and to prevent the syndrome of thoracic insufficiency[2]. The number of pulmonary alveoli grows rapidly until the age of 2 years, and then continues to increase at a slower rate until the age of 8 years. After this age the cells increases in size but not in number[3]. Therefore, any deformation or reduction in the elasticity of the thoracic cage affects the development of the respiratory parenchyma and therefore the respiratory function. The restriction of the lung parenchyma causes arterial pulmonary hypertension that leads to life-threatening diseases, i.e. pulmonary heart, heart failure[4]. This pathological condition is called syndrome of thoracic insufficiency. It seems that there is a direct correlation of respiratory function with the level of the T1-T12 vertebrae, in children who were subjected to spinal fusion due to congenital scoliosis. In these children a decrease of the pulmonary vital capacity of 50% was observed after spinal fusion. In fact, in children younger than 8 years of age who were subjected to spinal fusion, the vital capacity decreased by 60%. These studies revealed that the height of T1-T12 must be greater than 20 cm in order to avoid the syndrome of thoracic insufficiency[5]. Therefore, in these ages spinal fusion is prohibitive because it reduces the vital capacity of the lungs. The spinal fusion, also, decreases the elasticity of the thoracic cage, which acts negatively on the respiratory function[6,7]. In addition, in children of this age, with a great expectancy of growth, treatment with posterior instrumented spinal fusion can cause the crankshaft phenomenon. This is a new rotation deformity that develops after spinal fusion, due to the growth of the body of the vertebra, which cannot be restrained by the posterior instrumented spinal fusion. Last contraindication for spinal fusion in early scoliosis is the asymmetry of the torso-limb that can be caused by the spinal fusion.

Treatment

Conservative treatment

The conservative treatment has poor results in terms of evolution of childhood scoliosis because it can't stop the progression of scoliosis. However, it is a useful tool because a) it can help the patient with hypotonia stay in the sitting position, b) it can control the secondary curves in patients with congenital scoliosis and c) it saves us some time before deciding upon a more active intervention[1]. For the conservative treatment brace of the spine, thermoplastic seat, back props, and casts of the spine can be used. In addition, special physical therapy programs such as SCHROTH, SEAS, and SCOLISMART can be helpful. The brace of the spine can be hard or soft. The hard brace is the most widely used and documented over time. The

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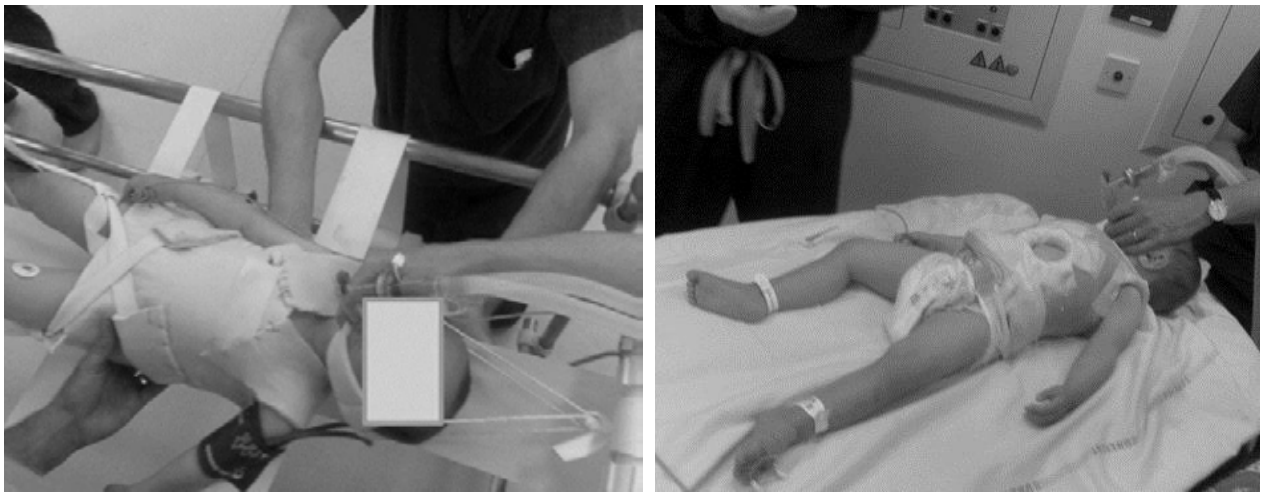

Figure 2. *Procedure of serial casting for early onset scoliosis.*

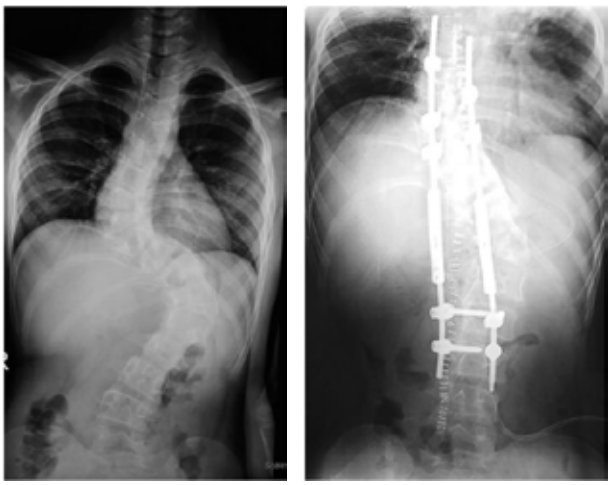

Figure 3. *A young girl of 10 years with neurofibromatosis treated with growing rods.*

most common type is the Boston and the Cheneau brace. Attempts have been made to treat the scoliosis with soft braces (i.e. Spinecor, Scolismart), but they did not prove their effectiveness. The traditional hard scoliosis braces can have some good results in idiopathic scoliosis and in some syndromic scoliosis with characteristics of idiopathic scoliosis. On the contrary, the hard brace has poor results in neuromuscular and congenital scoliosis. A brace for scoliosis, applied to a child less than 3 years old will need to be changed every 4 months due to the development of the spine. In adolescence the brace needs to be changed every 1 ½ years. This increases the costs of bracing during childhood. For this reason, in our clinic we have designed and used a type Boston or Cheneau growing brace which consists of two parts. The first part is applied to the pelvis, and the second part is applied to the torso and connects with the first part with three metal plates (**Fig. 1**). Using these plates, we can increase the brace's height every 4 months. We can repeat this increase in height 2-3 times, in order to keep the brace for 1 to 1 ½ years. These braces have been used since 2012 in 4 kids with success. In case that the scoliosis cannot be controlled by a brace, the next step is the use of a serial spinal cast. In this case, a plaster cast is placed to the child under general anesthesia. The child is placed at a type Cotrel-Dupusett table of traction and a plaster cast is applied. Special care is needed not to squeeze the viscera with the cast by creating windows of relief (**Fig. 2**). This cast needs to be changed every 2 months. The complications that can be observed with conservative treatment are pressure of the abdominal viscera, reduction in the glomerular filtration rate, a slight decrease in the volume of the lungs, tubular thorax, flattening of the lumbar spine and psycho-social disorders.

Surgical treatment

When the conservative treatment is unsuccessful surgical treatment is needed. Surgical treatment at this age includes systems of correction of the spine with-

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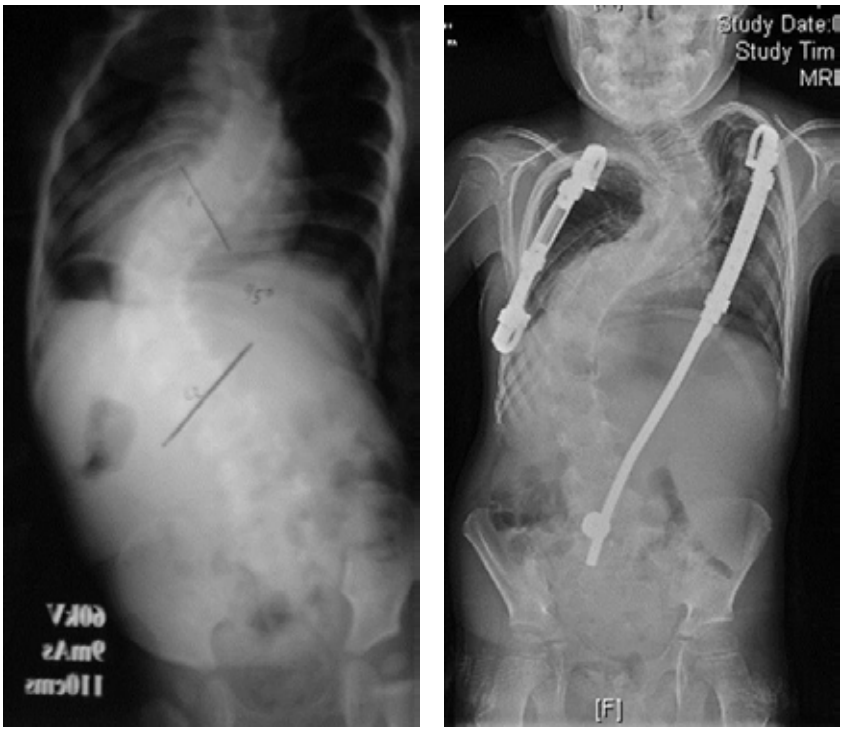

Figure 4. *A young boy of 5 years old treated with the VEPTR system.*

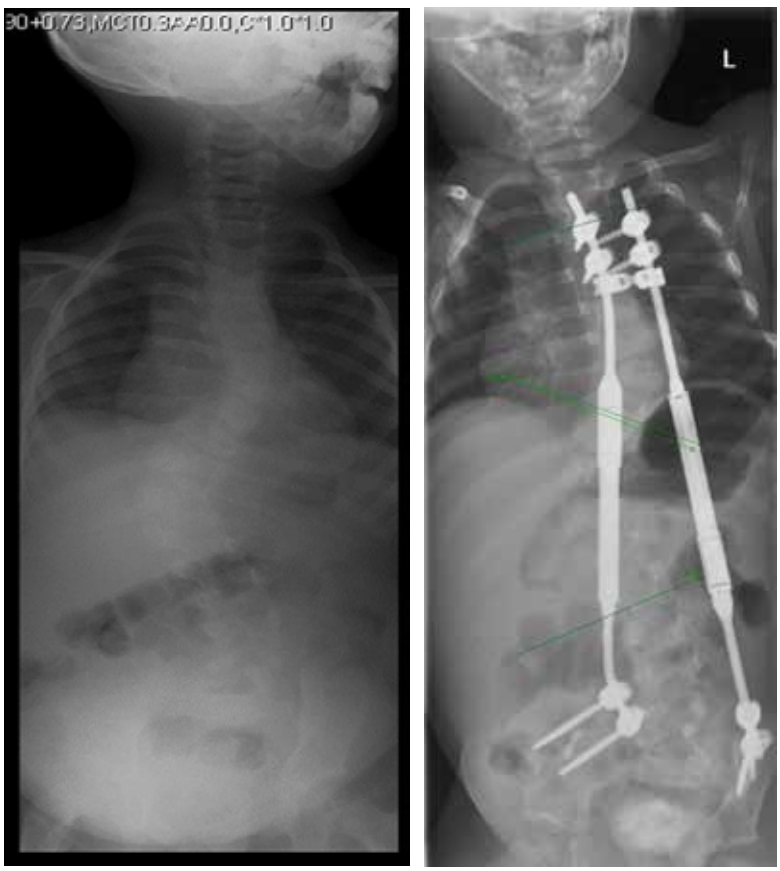

Figure 5. *A young boy of 3 ½ years old with Stickler syndrome treated with MAGEC system (courtesy by Colin Nnadi).*

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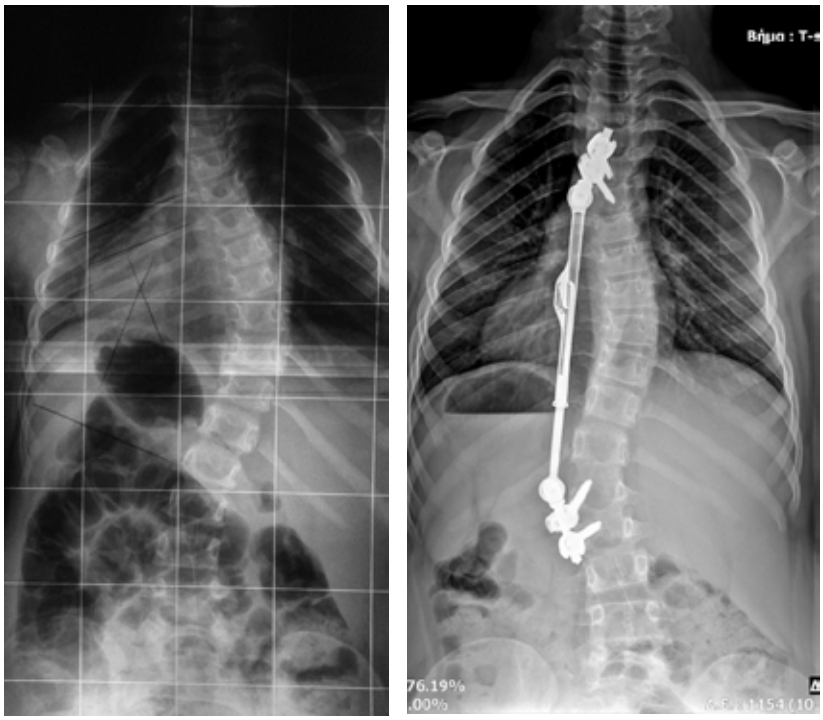

Figure 6. *A girl of 8 years old treated with Apifix EOS system.*

out spinal fusion. These systems can be divided into three categories: systems with growing rods, systems with guided rods and compression-based systems[1,9].

The traditional growing rods belong to the growing rods of the first category of systems, that need to be distracted, manually, every 6 months under general anaesthesia. This system is placed by posterior approach by pedicle screws at two vertebrae above and two below the scoliosis. The rods have a mechanism that allows lengthening (**Fig. 3**). The fixation of the rod to the vertebrae, other than screws, can be done with hooks, sublaminar wires (or straps), or with rib rings. The most powerful support is achieved with the pedicle screws. Each support system has its biomechanical peculiarities and it is useful to have alternative options in case it is not possible to place pedicle screw or because we need to preserve the elasticity of the correction system that we use. These traditional growing rods are the «gold standard» of surgical treatment of childhood scoliosis. The system VEPTR (Vertical Expandable Prosthetic Rib) also belongs to the first category of systems with growing mechanisms[8]. This system, basically, is a mechanism of stretching of the ribs. This system is fixed to the upper thoracic cage with rib rings and to the lower part of the scoliosis either with rib rings, pedicle screws or pelvic hooks (**Fig. 4**). The lengthening needs to be made manually every 4-6 months under general anesthesia. This system has limited effectiveness in the correction of scoliosis, but it is a good choice for patients with rib fusion and a restrictive chest cage (i.e. Jeune's Syndrome). In order to avoid recurrent surgeries in children, a new system, the MAGEC (Magnetic Expansion Control), has been designed. This is placed with pedicle screws like the classic growing rods, but the MAGEC rods have a magnetic mechanism that allows lengthening with a remote control at the outpatient department[10,11,12] (**Fig. 5**). Similarly, the APIFIX-EOS system was designed consisting of a self-growing rod that is placed in the concave side of the scoliosis by pedicle screws above and below the curve (**Fig. 6**)[13,14]. The lengthening of this rod is made mechanically with the movement of the torso and with special physical therapy. Also, a similar system, EURO V2, designed by Lotfi Miladi, is placed with special sacroiliac screws and

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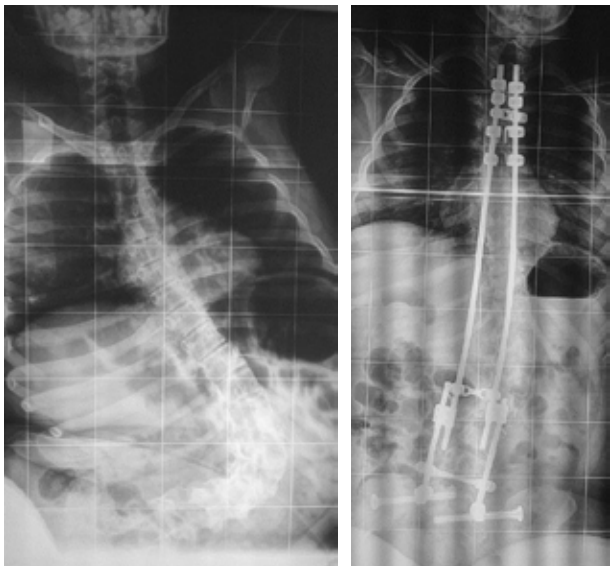

Figure 7. *A girl of 10 years old treated with EURO V2 system.*

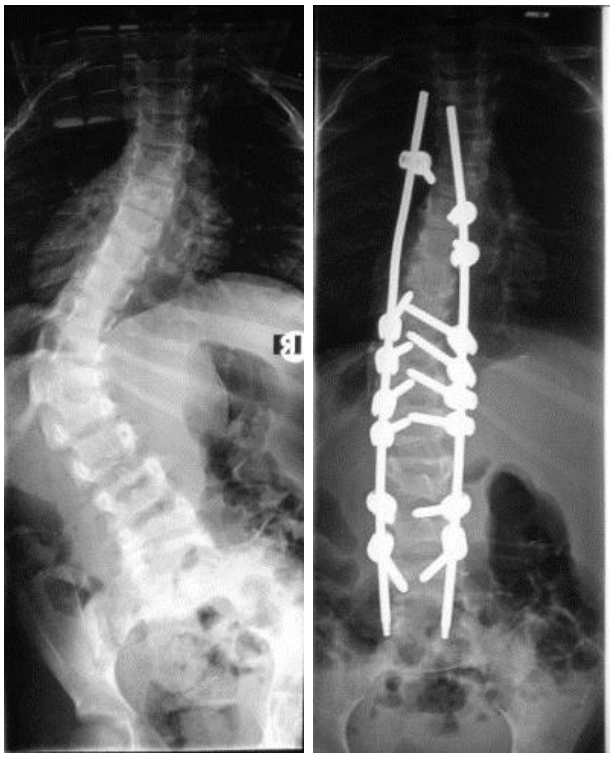

Figure 8. *A young boy with neurofibromatosis of 6 years old treated with Shilla system.*

4 hooks at the upper part of scoliosis. The rods have a mechanism that allows the lengthening following the growing of the spine (**Fig. 7**).

In the second category includes the guided rods. The Luque-Trolley was the first system of this class and consists of two rods which are fixed in the spine with sublaminar wires. The wires can slip on the rod following the growing of the spine. This system is low cost and used since the 1970s with satisfactory results. However, the extensive subperiostal approach that needs to be done to place it can lead to early spontaneous spinal fusion. Later systems such as the Shilla[15,19] and the Modern Trolley are placed with a minimal approach. The system of Shilla has special pedicle screws that slide on the rod, like the sublaminar wires (**Fig. 8**), while the Modern Trolley is consists of pedicle screw with a head from polyester that are connected to and slip on the rods.

The third category includes the compression-based systems: Vertebral Body Stapling[20] and Vertebra Body Tethering[21]. These systems affect the growth of the spine by hemiepiphysiodesis in a similar way as in the treatment of varus or valgus knee. The hemiepiphysiodesis includes the curved part of the scoliosis in order to stop the growing of the convex side of the spine and to leaves the concave side free to grow correcting the scoliosis. The hemiepiphysiodesis of the vertebrae can be made with buckles (stapling) or dynamic fusion systems (tethering) which are placed by anterior approach (open or thoracoscopic). These systems modify the growing of the vertebra and use the viscoelastic properties of the intervertebral disc to correct the scoliosis. Therefore, these systems are used also for adults.

The materials of all these systems implemented at children without a spinal fusion undergo continuous forces because they are not protected by a spinal fusion. For this reason, these systems are prone to complications of failure of materials such as fracture of the rod (15%) and failure of the upper support (up to 95%)[16,17,18]. Breakage of the pin of the magnetic mechanism has been observed with the use of the magnetic rod (MAGEC). With the compression systems subcorrection or overcorrection of scoliosis has been observed, because it is difficult to calculate the correct age to use these systems.

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Also, breakage of the connective belt between the screws has been observed with these systems. The surgical revision of these systems is particularly difficult due to the anterior approach. Metallosis of growth-guided systems has been observed due to friction of materials. Another complication that may occur is wound infection (6.7%, of which 67% will need surgical debridement). Other complications include early spontaneous spinal fusion (that may occur due to the surgical approach), and junctional kyphosis (that may occur due to the sagittal imbalance and due to the increased «hardness» of the stabilized part of the instrumented spine). Although the new systems do not require regular revisions per semester, they may often need non-scheduled re-operations but, these are fewer compared to these needed with the classical system. We always need to bear in mind is the psycho-social consequences of the repeated operations to the children.

Conclusion

The treatment of early onset scoliosis is a challenge because of the need to correct the deformity of the spine avoiding the spinal fusion with the traditional systems. The new systems offer new options to treat children with scoliosis and avoid the spinal fusion. Still the perfect system has not been invented. Every spine surgeon has to choose the system he is going to use to each individual child, and hence choose the complications he will encounter. A

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

REFERENCES

1. Early-onset scoliosis – Current treatment. V. Cunin. Orthopaedics & Traumatology: Surgery & Research, 2015
2. Vitale MG, Matsumoto H, Bye MR, et al. A retrospective cohort study of pulmonary function, radiographic measures, and quality of life in children with congenital scoliosis: an evaluation of patient out comes after early spinal fusion. Spine 2008
3. Canavese F, Dimeglio. A normal and abnormal spine and thoracic cage development. World J Orthop 2013
4. Swank SM, Winter RB, Moe JH. Scoliosis and cor pulmonale. Spine 1982
5. Dimeglio A, Canavese F. The growing spine: how spinal deformities influence normal spine and thoracic cage growth. Eur Spine J 2012
6. Emans JB, Ciarlo M, Callahan M, Zurakowski D. Prediction of thoracic dimensions and spine length based on individual pelvic dimensions in children and adolescents: an age-independent, individualized standard for evaluation of outcome in early onset spinal deformity. Spine 2005
7. Campbell Jr RM, Smith MD. Thoracic insufficiency syndrome and exotic scoliosis. J Bone Joint Surg Am 2007
8. Motoyama EK, Yang CI, Deeney VF. Thoracic malformation with early-onset scoliosis: effect of serial VEPTR expansion thoracoplasty on lung growth and function in children. Paediatr Resp Rev 2009
9. Skaggs DL, Akbarnia BA, Flynn JM, et al. A classification of growth friendly spine implants. J Pediatr Orthop 2014
10. Miladi L, Dubousset J. Magnetic powered extensible rod for thorax or spine. In: Akbarnia BA, Yazici M, Thompson GH, editors. The growing spine: management of spinal disorders in young children. Berlin, Heidelberg: Springer-Verlag; 2010
11. Cheung K, Cheung JP, Samartzis D, et al. Magnetically controlled growing rods for severe spinal curvature in young children: a prospective case series. Lancet 2012
12. Akbarnia BA, Cheung K, Noordeen H, et al. Next generation of growth-sparing techniques. Preliminary clinical results of a magnetically controlled growing rod in 14 patients with early-onset scoliosis. Spine 2013
13. Sekouris N, Pilichou A, Sovatzoglou A, Soultanis K, Karavidas N, Flouda L, and Vlachos E. The Apifix Automatic Self-Correction Technique for Adoles-

VOLUME 70 | ISSUE 2 | APRIL - JUNE 2019

cent. Idiopathic Scoliosis at 1 ½ Years Follow-Up: A Preliminary Report. Global Spine; Issue S 01, 2016
14. Armin U, El-Hawary R, Betz R, Lonner B, Floman Y. Preclinical Bench Testing on a Novel Posterior Dynamic Deformity Correction Device for Scoliosis. Spine Deformity 2019 (7) p 203-212
15. Sekouris N, Pilihou A, Vlahos E, Soultanis K, Sapkas G, Flouda L. The Shilla Growth Guidance Technique for Paediatric Scoliosis at 3-year Follow-up: a Preliminary Report. Global Spine Journal; Issue S 01, 2016
16. Skaggs KF, Brasher AE, Johnston CE, et al. Upper thoracic pedicle screw loss of fixation causing spinal cord injury: a review of the literature and multicenter case series. J Pediatr Orthop 2013
17. Sankar WN, Skaggs DL, Yazici M, et al. Lengthening of dual growing rods and the law of diminishing returns. Spine 2011
18. Yazici M, Olgun ZD. Growing rod concepts: state of the art. Eur Spine J2013
19. McCarthy RE, Luhmann S, Lenke L, McCullough FL. The Shilla growth guidance technique for early-onset spinal deformities at 2-year follow-up: a preliminary report. J Pediatr Orthop 2014
20. Marks DS, Iqbal MJ, Thompson AG, Piggott H. Convex spinal epiphysiodesis in the management of progressive infantile idiopathic scoliosis. Spine 1996
21. Betz RR, Kim J, D'Andrea LP, Mulcahey MJ, Balsara RK, Clements DH. An innovative technique of vertebral body stapling for the treatment of patients with adolescent idiopathic scoliosis: A feasibility, safety, and utility study. Spine 2003

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Sekouris N, Paspati I, Fligger I, Flouda L. Spinal deformity in children. *Acta Orthop Trauma Hell* 2019; 70(2): 57-64.

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CASE REPORT

Bizarre parosteal osteochondromatous proliferation (Nora's lesion) affecting the distal end of femur: a case report and review of the literature

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ABSTRACT

Bizarre parosteal osteochondromatous proliferation (BPOP) or else Nora`s lesion, as it is commonly known, was first described by a pathologist named Nora in 1983. Typically this rare disease is occurred in the small tubular bones of the hands and feet and especially in the proximal and middle phalanges as well as the metacarpal and the metatarsal bones. Here we present a case of a young female with a distal femur lesion originally thought to be an exostosis. A 19-year old, Caucasian female was referred to our outpatient clinic complaining of pain at her right femur. Plain x-rays revealed a 1.25cm, well – delimited, ossified, rounded mass with edema around it. Computed tomography showed a lesion in contact with the femoral metadiaphysis and surrounding by a slight thickening of the cortex. This lesion was more compatible with the presence of an exostosis. Based on the magnetic resonance imaging, the clinical and radiological findings the lesion seemed to represent BPOP. The isotope bone scan showed nothing pathological in other regions of the skeleton. The patient was taken to the operating room for resection of her bone lesion. The diagnosis of BPOP was confirmed by pathologic examination.

KEY WORDS: Bizarre parosteal osteochondromatous proliferation (BPOP); Nora's lesion; Femur

Introduction

Bizarre parosteal osteochondromatous proliferation (BPOP) or else Nora`s lesion, as it is commonly known, was first described by a pathologist named Nora in 1983 [1]. His paper about this unique lesion was first published in The American Journal of Surgical Pathology and reported 35 cases of BPOP of the hands and feet [1]. Since then, over 200 cases of Nora`s lesion have been presented in the literature, very few of which have affected the femur as

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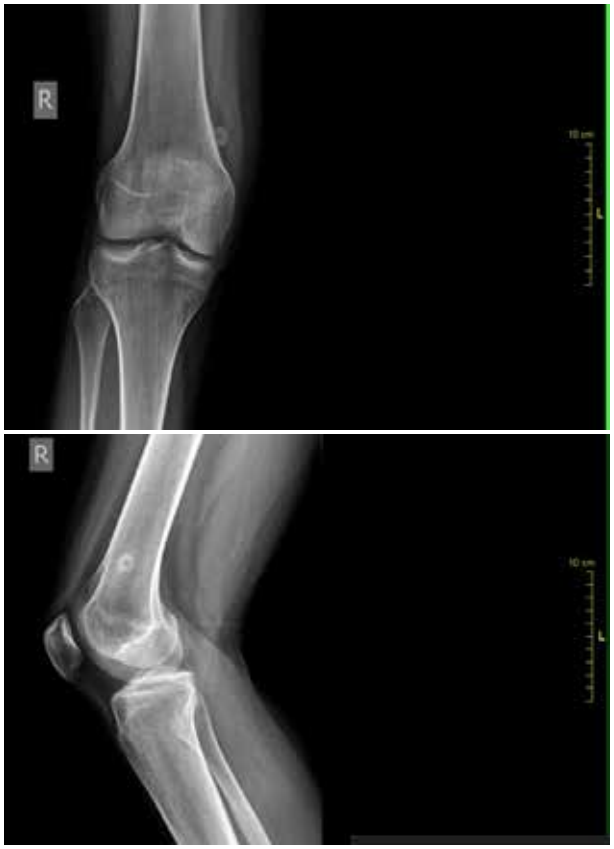

Figure 1: *Initial anteroposterior and lateral femur radiographs demonstrating a 1.25cm, well – delimited, ossified, rounded mass that was arising from the medial cortical aspect of the distal third of femoral diaphysis, above the medial femoral condyle*

in the case of our patient.

Typically this rare disease is occurred in the small tubular bones of the hands and feet and especially in the proximal and middle phalanges as well as the metacarpal and the metatarsal bones [1]. But other more uncommon sites have been described. In 1993, almost 10 years after Nora, Meneses reported 65 cases of bizarre periosteal osteochondro-matous proliferation [2]. Seventeen out of these cases involved the long bones. Six lesions involved the ulna, three the radius and the femur and two the tibia and the fibula. Even more rare sites that have been reported in the literature are the mandible, maxilla, sks skull and the sesamoid bones [2, 3, 4, 5].

Nora's lesion is occurred to a wide range of age.

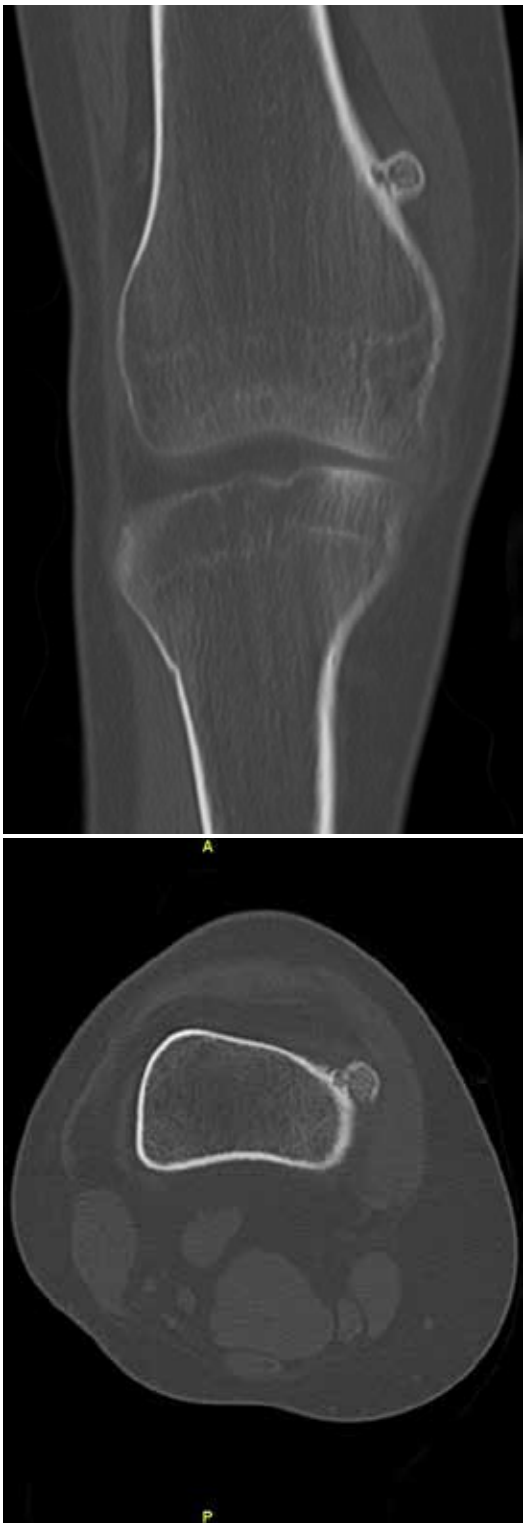

Figure 2: *CT findings. Coronal and axial images show a lesion in contact with the medial aspect of the femoral metadiaphysis, surrounded by cortex. Around the lesion was recognized a slight thickening of the cortex*

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Luigia Abramovici reported a range from 12 to 63 years with an average age of 30.3 years [6]. Meneses reported cases from 8 to 73 years old with an average of 33, 9. [2]. All authors agree that it is more usual during the third and fourth decade of life. Our patient was 19 years old when she came to our outpatient clinic. She experienced pain for the last six months to the medial aspect of her distal femur. Before this period she had not felt any pain or made any test to her femur so we cannot be sure when this lesion started growing or the rate which it had been growing

Case presentation

A 19-year-old woman presented to our outpatient clinic complaining of pain at her right femur. She could localize it particularly to the medial aspect of her distal femur. The pain was present almost every night, with no apparent trigger the last year. The patient referred that the last six months this could easily be reproduced with palpation. She denied any injury at her femur the last years and she had no history of any prior surgical intervention.

Clinical examination revealed a non-tender and non-mobile mass at the medial aspect of her distal femur. It was painful at palpation and her knee had a full range of active and passive motion.

Standard radiographs showed a 1.25cm, well-delimited, ossified, rounded mass that was arising from the medial cortical aspect of the distal third of femoral diaphysis, above the medial femoral condyle (**Fig. 1**). An impression of an edema of the soft tissue in the area was given.

Computed tomography revealed a clearly visible lesion in contact with the medial aspect of the femoral metadiaphysis, surrounded by cortex and exhibiting a maximum cranial-caudal diameter of approximately 8mm. Around the lesion was recognized a slight thickening of the cortex (**Fig. 2**). This lesion was more compatible with the presence of an exostosis and it was located medially of the vastus medialis.

On magnetic resonance imaging (MRI), the margins of the lesion had a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted image (**Fig.3**). Based on the clinical and radiological findings, the lesion was felt to represent BPOP.

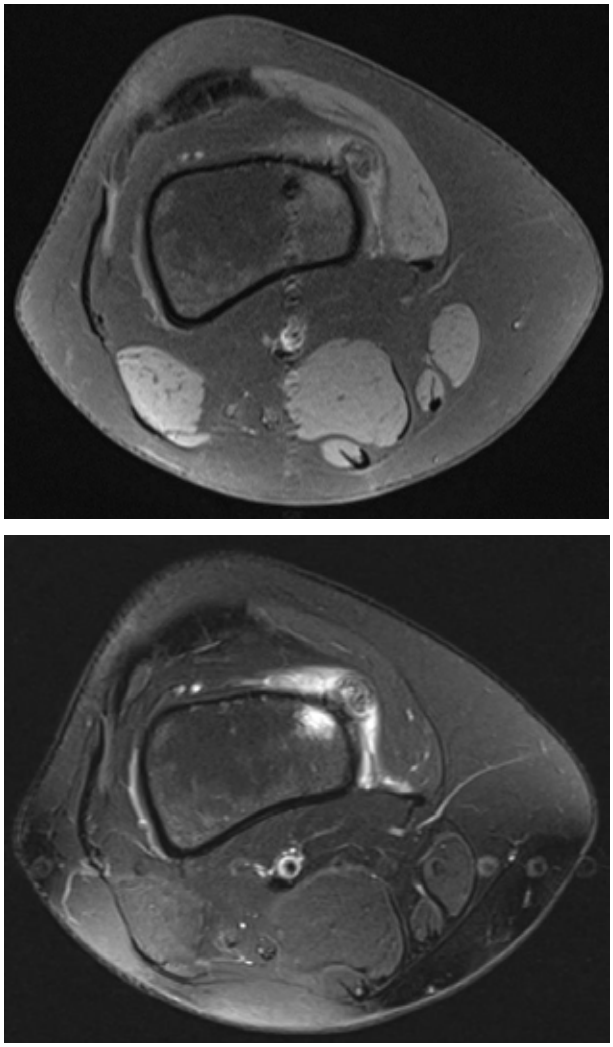

Figure 3: *MRI findings. An axial T1-weighted MRI image that shows a low signal intensity at the margins of the lesion. An axial T2-weighted MRI image that shows a high signal intensity at the margins of the lesion.*

During the first phase of the isotope bone scans noted no pathologic concentration of the radiopharmaceutical in the examined area. In the second and third phases there was an increased and well delimited concentration - fixation of the radiopharmaceutical in the medial area of the femoral metadiaphysis. From the remaining skeleton nothing pathological was observed (**Fig. 4**).

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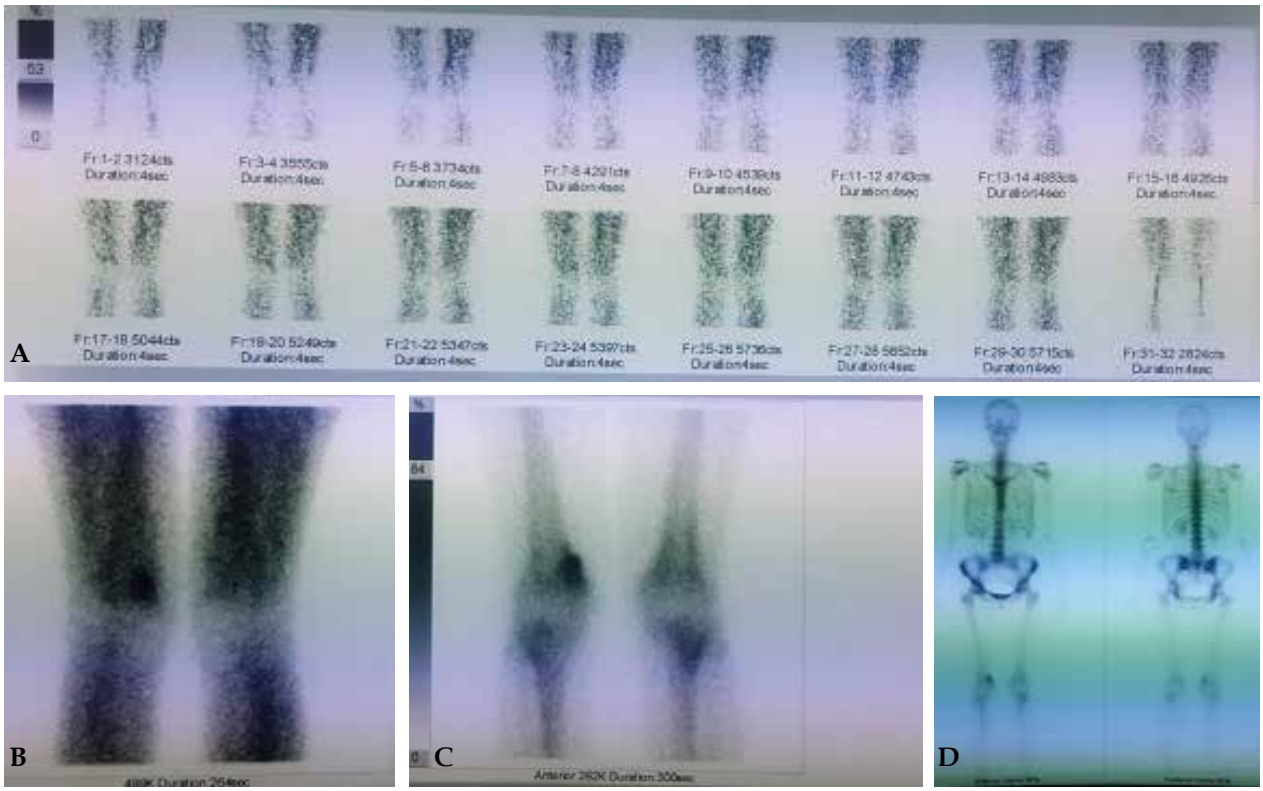

Figure 4: *A First phase, B intermediate phase, C delayed phase and D whole-body flash views of the isotope bone scan. No pathologic concentration of the radiopharmaceutical during the first phase. In the second and third phases, there was an increased and well – delimited concentration – fixation of the radiopharmaceutical in the medial area of the femoral metadiaphysis. From the remaining skeleton nothing pathological was observed.*

The patient underwent an excision of the femoral mass twelve months after the initial symptoms. The mass was identified through a medial approach under the medial vastus. The surface of the

the lesion was found to be covered by a cartilage cap and its interior to be composed of osteoid tissue in continuity with the cortical bone. The mass was excised with an osteotome and the abnormal area of underlying bone was decorticated (**Fig. 5**).

The gross and the microscopic examination revealed a reactive type of lesion consisting of bone and a cartilaginous hood on the surface of the bone. The cartilageous plaque was rich of cells, the chondrocytes appeared to be enlarged and some of them binucleated. On the base of the plaque there was an endochondral ossification with blue calcification (stained with hematoxylin and eosin) at the junction point. Osteoid had a prominent osteoblastic edge, while the intermediate spaces contained capillaries and loose layer. Moreover, it was noticed a spindle cell proliferation between bony trabeculae without atypia. These findings confirmed the diagnosis of BPOP.

Discussion

Bizarre parosteal osteochondromatous proliferation affects both sexes the same. In all the literature, we have found no difference between males and females in any research [2].

Data on symptoms are scarce. Most of the cases are asymptomatic or there is a pain during palpation of the lesion [1, 6]. Sometimes the authors correlate the tenderness with a quicker growth of the lesion [1]. More symptoms are reported and they depend on the site and the size of the tumor and the anatomical structures that are near. Varun K. Bhalla reported a case of a young child with a Nora's le-

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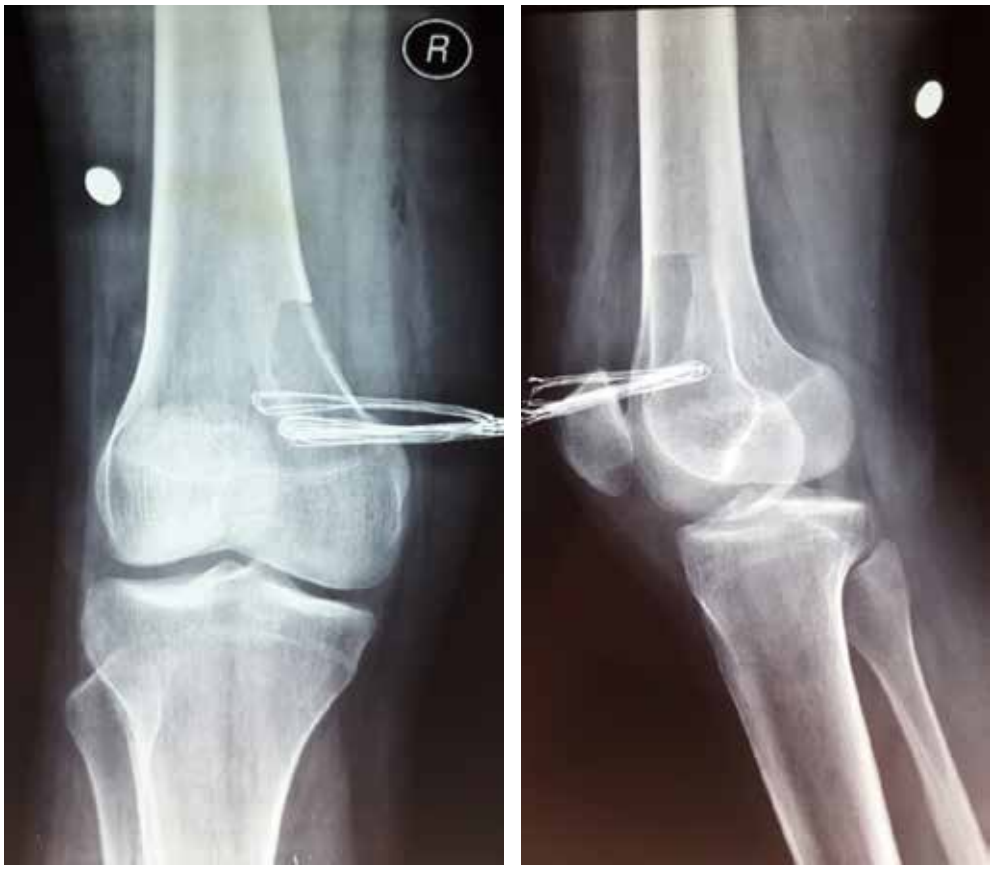

Figure 5: *Postoperative anteroposterior and lateral femur radiographs demonstrating resection of the mass.*

sion on his distal femur that caused a popliteal artery pseudoaneurysm [7]. Beverlie L. Ting reported a case report of BPOP lesion of the ulna that caused an erosion of the adjacent radius [8]. Due to the fact that it is usually asymptomatic, most times it is discovered incidentally. A percentage of patients report prior trauma on the site of the growth but it is confirmed as a triggering factor by any research [9].

The radiologic findings of BPOP is useful to differentiate them from osteochondromas [1]. This benign tumor arises directly from the cortical surface of the bone and has no communication with the medulla. As a result, it does not disturb the architecture of the bone [6]. The lesions are usually calcified and they resemble as a soft-tissue tumor like mass that is attached to the bony cortex [10, 2]. Nora's lesion can be observed in plain radiographs but because of its soft tissue nature it can be very useful to perform an MRI test on the patient.

Despite the clinical and radiographic characteristics of this disease, the diagnosis can only be obtained through a biopsy and a histological examination. The size is usually from 0.3 to 3cm [1].

The histologic findings are firstly an irregular maturation of cartilage into bone that produces chondro-osteoid that has a characteristic blue quality and it is often called blue bone. Secondly it contains large bizarre binucleated chrondrocyte that often matures into bone. Lastly, it can be noticed a spindle cell proliferation between bony trabeculae without atypia [1, 2, 6].

The common treatment of this disease requires surgery and it is a complete excision of the lesion. It has high recurrence rates ranging from weeks postoperatively to years [2, 6]. Despite this fact and its sometimes-aggressive outgrowth, it is a benign tu-

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mor. There are no reports of malignant conversion, metastases or correlated diseases or deaths because of this disease in the literature [11]. In our patient the whole mass was excised and the underlying bone was decorticated. We preferred this method so that we can reduce the possibility of recurrence. Follow up was up to two years in our outpatient clinic. No pain was reported during this period. The patient had no complications because of the surgery. Two years after the operation, the patient was contacted by telephone and no symptoms were mentioned.

In summary, bizarre parosteal osteochon-dromatous proliferation is a benign tumor-like lesion that has a characteristic radiographic and histologic appearance. It is usually asymptomatic but it needs surgical removal so it can be differentiated from other malignant tumors. It has great rates of recurrence so it is very important to follow up the patient for a period of time in order to diagnose it.

Conflict of interest:
The authors declared no conflicts of interest.

REFERENCES

1. Nora FE, Dahlin DC, Beabout JW et al. , Bizarre parosteal osteochondromatous proliferations of the hands and feet, Am J SurgPathol, 1983.
2. Meneses MF, Unni KK, Swee RG et al., Bizarre parosteal osteochondromatous proliferation of bone (Nora's lesion), Am J SurgPathol. 1993.
3. Dashti HM, Reith JD, Schlott BJ et al., Bizarre parosteal osteochondromatous prolifera-tion (Nora's Lesion) of the mandible. a rare bony lesion, Head Neck Pathol , 2012.
4. Nobusawa A, Sano T, Neqishi A et al., Bizarre parosteal osteochondromatous proli-feration of the maxilla: a case report, Oral Surg Oral Med Oral Pathol Oral Radiol , 2012.
5. Berber O, Dawson-Bowling S, Jalqaonkar A et al., Bizarre parosteal osteochondromatous prolife-ration of bone: clinical management of a series of 22 cases, J Bone Surg Br, 2011.
6. Abramovici L, Steiner GC, Bizarre parosteal osteochondromatous proliferation (Nora's lesion): a retrospective study of 12 cases, 2 arising in long bones, Hum Pathol , 2002.
7. Bhalla VK, Coulson H, Parker w et al., Popliteal pseudoaneurysm caused by Nora's lesion of the femur in a young child: a rare presentation and first report, J PediatrSurg , 2012.
8. Tinq BL, Jupiter JB, Recurrent bizarre parosteal osteochondromatous proliferation of the ulna with erosion of the adjacent radius: case report, J Hand Surg Am, 2013.
9. Kershen LM, Schucany WG, Gilbert WG, Nora's lesion: bizarre parosteal osteochondromatous proliferation of the tibia, Proc (BaylUniv Med Cent), 2012.
10. Rybal LD, Abramovici L, Kenan S et al., Corti-co-medullary continuity in bizarre parosteal os-teo-chondromatous proliferation mimicking os-teo-chondroma on imaging, Skeletal Radiol, 2007.
11. Gruber G, Giessauf G, Leithner A, Bizarre parosteal osteochondromatous proli-feration (Nora lesion): a report of 3 cases and a review of the literature, Can J Surg, 2008.

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