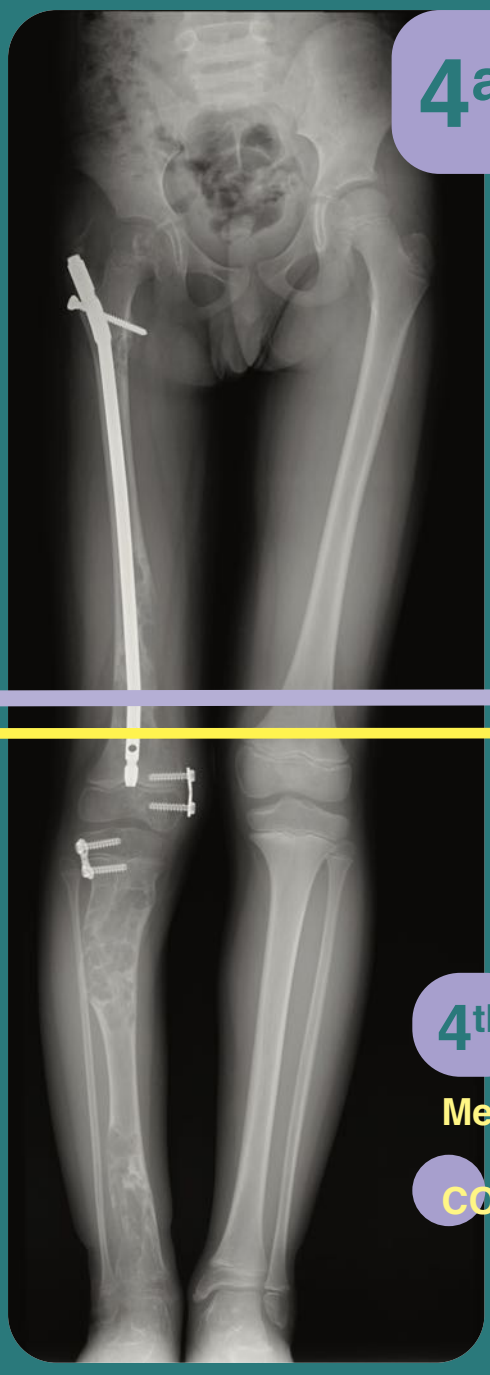

4as

Jornadas de Doenças Ósseas Raras

COIMBRA, 29 e 30 de junho de 2023

ISEC › Instituto Superior de Engenharia de Coimbra

Latitude 40°11'33.6"N | Longitude 8°24'41.8"W

4th

Meeting on Rare Bone Diseases

COIMBRA, June 29th - 30th 2023

LIVRO DE RESUMOS

Organização / Organization

– **Equipa Multidisciplinar de Doenças Ósseas Raras do Centro Hospitalar e Universitário de Coimbra (CHUC-ERN-BOND)**

Patrocínio científico

Apoios

Secretariado

Associação de Saúde Infantil de Coimbra

Caros/as Colegas,

Este livro abrange os resumos das comunicações a apresentar nas **4as J*ornadas de Doenças Ósseas Raras***, que se realizarão presencialmente em Coimbra nos dias 29 e 30 de junho de 2023.

Agradecemos a todos os que submeteram os seus trabalhos.

O nosso agradecimento também ao Prof. Jorge Saraiva, à Dra. Teresa Borges e ao Dr. José Poupino, que constituem a comissão científica de seleção das comunicações a premiar, e a todos os moderadores das diferentes sessões que contribuirão para a avaliação das comunicações.

Em nome da equipa multidisciplinar de displasias ósseas do CHUC,

Sérgio B. Sousa

Sessão I
C01

Unraveling osteogenesis imperfecta and its differential diagnosis – monocentric retrospective cohort study of 94 patients with clinical suspicion of osteogenesis imperfecta

Celia Azevedo Soares [1,2,3,4], *Anabela Bandeira* [5,6], *Rute Sousa Martins* [6,7], *Maria Abreu* [1]

Centro Hospitalar Universitário de Sto António

Introduction:
Osteogenesis imperfecta (OI) encompasses a range of diseases characterized by bone fragility and systemic manifestations. Diagnosing OI can be challenging due to its diverse clinical presentation and potential overlap with other causes of bone fragility. This study aimed to describe a large cohort of individuals with suspected genetic bone fragility, including those without confirmed OI.

Methods:
We retrospectively analyzed medical records of 94 patients with suspected OI at Centro Hospitalar Universitário de Sto. António.

Results:
Of the 94 patients, 47 were males and 47 were females, with a median age of 26 years (range: 3-76). Sixteen patients were lost to follow-up. Among the remaining 78 patients, 53 had a molecular diagnosis of OI (COL1A1: 39, COL1A2: 13, IFITM5: 1), while 22 patients did not have a final molecular diagnosis. Among the latter group, 13 underwent OI gene panel testing without identifying causal variants, two lacked OI-related familial variants, three were undergoing molecular testing for the first time, one declined testing, and three were awaiting additional genetic testing. In this subgroup, ten patients were still suspected to have OI, while three adults had idiopathic juvenile osteoporosis and three suspected syndromic bone fragility.

Conclusion:
This study provides insights into the clinical features and molecular diagnoses of a large cohort of patients with suspected genetic bone fragility. The challenges in diagnosing OI, especially in cases with overlapping causes of bone fragility, are highlighted. Further research is needed to enhance diagnostic approaches and identify the genetic basis in patients without confirmed OI

Sessão I
C02

RMRP-related spectrum – clinical and molecular characterization of ten Portuguese patients

C. S. Rosas[1], F. Ramos[1], L. Ramos[1,2], A. Mirante[3], A. Brett[4,5], S. Lemos[4], F. Regateiro[6,7,8], J. Azevedo[9], A. Cordeiro[10], J. Pereira[11], S. Modamio-Høybjør[12], K. E. Heath[12,13], S. B. Sousa[1,14]

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Background
Cartilage-Hair Hypoplasia (CHH) is a RMRP-related disorder comprising a continuum phenotypic spectrum characterized by metaphyseal dysplasia with disproportionate short stature and findings such as gastrointestinal dysfunction, immunodeficiency, increased risk for malignancy or anemia.

Methods
Clinical and molecular characterization of 10 CHH-spectrum cases from a Portuguese hospital centre based on the retrospective analysis of medical records.

Results
We describe 7 male and 3 female patients, from 8 unrelated families, with a CHH-spectrum diagnosis, currently between 1 and 50 years old. Prior to molecular study, most had suspected clinical or radiological diagnosis (7/10), from birth to 46 years of age. Two families had a skeletal dysplasia panel performed prenatally. In one, only one variant was detected. In the other the diagnosis was missed (RMRP not included in exome). Most patients have short stature (9/10), 4/5 with prenatal onset, normal occipitofrontal circumference (8/8), normal motor development (5/7), impaired lymphocyte proliferation (6/6) and 3/3 have reported recurrent or severe infections. Variable hypotrichosis was identified in 6/9 patients, 6/7 patients had gastrointestinal dysfunction or failure to thrive, one patient had severe hemolytic anemia and another persistent idiopathic thrombocytopenic purpura. No malignancies were reported. A total of 12 previously described RMRP variants were identified.

Conclusion
Our data are globally in accordance with the literature. In 2/10 cases, one of which without short stature, diagnosis was only achieved by reverse phenotyping. We aim to include patients from other Portuguese hospital centres. Detailed description of national CHH-spectrum patients cohorts contributes to awareness and better-informed counselling and management.

Sessão I
C03

Os desafios na reabilitação de crianças com Síndrome de Apert: apresentação de três casos clínicos

Ana Cavalheiro, Diogo Costa, Filipa Gonçalves, Rosa Amorim, Lurdes Palhau

Centro Hospitalar Universitário de Santo António

Introdução:
A Síndrome de Apert é uma síndrome polimalformativa, caracterizada por craniosinostose, hipoplasia da média face e sindactilia das extremidades1. A intervenção da Medicina Física e de Reabilitação é essencial na melhoria dos défices motores, alterações da deglutição, fala e desenvolvimento. Apresentamos três casos de crianças diagnosticadas com Síndrome de Apert seguidas no nosso centro.

Casos Clínicos:
Relatamos os casos de duas meninas de 10 anos e 1 ano (caso A e B, respetivamente) e um menino de 1 ano (caso C) com síndrome de Apert. Todos foram submetidos a cirurgia de correção das coanas e os doentes A e C a correção da craniosinostose.
Nos doentes A e C detetamos um atraso no desenvolvimento motor, nomeadamente idade da marcha retardada (doente A aos 20m; doente C sem marcha) e atraso da fala e linguagem. Já a doente B apresentava dificuldades na alimentação (alimentada por gavagem durante primero mês).
Estes doentes integraram precocemente um programa de reabilitação nas valências de fisioterapia e terapia da fala. Em todos estes doentes temos observado uma evolução global positiva, sendo que a doente A é alimentada por vida oral e tem marcha autónoma, a doente B tem marcha autónoma, evolução ponderal e interação social adequadas, e o doente C apenas senta sem apoio e iniciou a introdução de sólidos.

Discussão/Conclusão:
A síndrome de Apert é uma doença rara, cujo tratamento exige articulação entre várias especialidades. Realça-se a importância do tratamento de reabilitação para otimização dos resultados cirúrgicos, estimulação do desenvolvimento psico-motor e prevenção de complicações associadas à disfagia.

Horizontal Gaze Palsy with Progressive Scoliosis – a case report

Adriana Correia[1], Mafalda Pires[2], Rita Fernandes de Jesus[1], Rita Amado Francisco[2]

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Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare congenital disorder characterized by absence of conjugated horizontal eye movements with preserved convergence and vertical gaze, and progressive scoliosis developing in early childhood and adolescence. It is an autosomal recessive syndrome that occurs due to mutation in ROBO3 gene.

Case presentation:
A 5-year-old female child from Fogo Island, Cape Verde, presented to a Physical Medicine and Rehabilitation consultation for scoliosis management. The parents are healthy, non-consanguineous and reported a normal and supervised pregnancy. The onset of progressive scoliosis was noted at 5 months of age. Physical examination revealed a severe right-sided thoracic scoliosis and absence of horizontal eye movements with preserved vertical gaze. No other neurological findings were observed. The full-spine X-ray confirm a right-sided thoracic scoliosis with a Cobb angle measuring 97.3º and grade II vertebral rotation. Due to the severity of the scoliosis, the patient underwent corrective surgery. The co-occurrence of horizontal gaze palsy and progressive scoliosis raised a high degree of suspicion for HGPPS. Consequently, the patient was referred to a genetic consultation for diagnosis confirmation and is currently awaiting the results of the genetic tests.

Conclusion:
This case report emphasizes the importance of early recognition and multidisciplinary management of HGPPS in pediatric patients presenting progressive scoliosis and horizontal gaze palsy. Although the condition is rare, timely diagnosis and appropriate interventions can help optimize the functional prognosis of patients affected by this condition.

Sessão I
C05

Neonatal bone fragility caused by EMILIN1 deficiency

Elsa Lucas-Castro[1,2], Fernando Santos-Simarro[1,2], Manuel Parrón-Pajares[2,3], Ana Coral Barreda-Bonis[2,4] , Dolores Elorza-Fernandez[2,5] , Karen E. Heath[1,2,6]

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Introduction:
Fractures observed during the neonatal period often lead to the investigation of whether they were due to non-accidental injury (NAI) or a genetic disorder.

Case report:
Firstborn of healthy nonconsanguineous parents, born full-term via spontaneous vaginal delivery. Admitted to hospital at 7-days old due to cephalohematoma. CT scan and X-rays revealed multiple complex cranial fractures and rib fractures. NAI protocol was discussed in our hospital and with international experts. Although the later agreed on NAI, it was no implemented as the neonate had thin, hyperelastic skin and a new fracture whilst in hospital care. Additional fractures were observed during the first month of life. Further medical examinations revealed aortic tortuosity and pulmonary artery stenosis, successfully corrected without complications. Now 6-years old, he has aortic tortuosity and hyperelastic skin but no further fractures.

Genetic studies:
Skeletal dysplasia panel performed during neonatal period. Subsequently, trio-based whole-exome sequencing (WES) was performed.

Results:
No variant of interest was identified in the panel nor in the initial WES but reanalysis in December 2022 revealed a homozygous frameshift variant in EMILIN1 which occurred due to paternal uniparental disomy for chromosome 2.

Conclusions:
1. EMILIN1 deficiency explains the child's clinical phenotype.
2. Biallelic EMILIN1 variants have been recently reported to cause cutis laxa, arterial tortuosity, aneurysm formation, and bone fragility (Am J Hum Genet. 2022;109(12):2230-2252). Profound bone fragility was reported in some cases during neonatal period.
3. Thus, although rare, this connective tissue disorder should be considered if fractures are detected during the neonatal period.

Sessão I
C06

Touraine-Solente-Gole syndrome: pathogenic variant in SLCO2A1 presented with polyarthralgia and digital clubbing

Rafaela Nicolau [1,2*] , *Tiago Beirão* [3] , *Francisca Guimarães* [4] , *Francisca Aguiar* [2,5] , *Sara Ganhão* [5] , *Mariana Rodrigues* [2,5] , *Ana Grangeia* [6] , *Iva Brito* [2,5]

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Background:
Primary Hypertrophic Osteoarthropathy (PHO), also known as Touraine-Solente-Gole Syndrome, is a rare, multisystemic autosomal recessive disorder caused by pathogenic variants in HPGD or SLCO2A1 genes. PHO usually starts in childhood or adolescence, presenting with digital clubbing, osteoarthropathy, and pachydermia. We described a complete form of the syndrome in a male patient with a homozygous variant in the SLCO2A1 gene (c.1259G>T).

Case presentation:
A 20-year-old male was referred to our Pediatric Rheumatology Clinic with a 5-year history of painful and swollen hands, knees, ankles and feet, prolonged morning stiffness and relief with non-steroidal antiinflammatory drugs. He also reported late onset facial acne and palmoplantar hyperhidrosis. Family history was irrelevant and parents were non-consanguineous. On clinical examination, he presented clubbing of the fingers and toes, moderate acne and marked facial skin thickening with prominent scalp folds. He had hand, knee, ankles and feet swelling. Laboratory investigation showed elevated inflammatory markers. Complete blood count, renal and hepatic function, bone biochemistry were normal, as well as immunological panel. Plain radiographs revealed soft tissue swelling, periosteal ossification and cortical thickening of the skull, phalanges, femur and toe acroosteolysis. Due to the absence of other clinical signs suggesting a secondary cause, we suspected PHO. A genetic study revealed a likely pathogenic variant, c.1259G>T (p.Cys420Phe), in homozygosity in the SLCO2A1 gene, thus confirming the diagnosis.

Conclusions:
To the best of our knowledge, this is the second genetically confirmed case of PHO in a Portuguese patient (first variant c.644C>T), both made at our department.

Sessão I
C07

Impact of respiratory rehabilitation in patients with skeletal dysplasia – a case report

Francisca Melo Ferreira[1], Lurdes Rovisco Branquinho[1], Carla Hovenkamp[1], Ana Margarida Ferreira[1], João Paulo Branco[1,2]

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Patients with skeletal dysplasia face daily challenges, namely in terms of self-care, mobility, effort tolerance, carrying out household tasks, social participation and leisure. These challenges limit the functionality and significantly affect the quality of life of these patients.

Rehabilitation, understood as a dynamic process through which the individual with a disability acquires the knowledge and technical skills necessary for an optimized physical, psychological and social function, is therefore one of the key pillars in the follow-up of patients with skeletal dysplasia.

We present the clinical case of a 42-year-old man, active worker, with autonomy for all activities of daily living. He was referred to the Physical Medicine and Rehabilitation department with the probable diagnosis of Bruck Syndrome 2, still without molecular confirmation. On physical examination, he showed kyphoscoliosis and a marked thoracic deformity that made him tired for medium efforts. The spirometry revealed the presence of a restrictive syndrome. The patient was integrated into a respiratory rehabilitation program with the aim of optimizing ventilatory dynamics, reconditioning to effort and strengthening of the respiratory muscles with monitoring through the Power Breath software. At the end of 10 sessions, a new spirometric study was carried out, which revealed improvements in forced vital capacity, forced expiratory volume and peak expiratory flow.

In patients with skeletal dysplasia, respiratory rehabilitation should be understood as an essential tool for maintaining lung function with a considerable impact on functionality and, consequently, on the quality of life of patients.

Cherubism in three siblings: a multidisciplinary approach

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Objectives:
Cherubism is a rare disease, characterized by the development of bilateral and symmetrical fibro-osseous lesions usually limited to the jaw bones, that can expand and give patients the characteristic cherubic facial appearance. In most patients, cherubism is due to dominant mutations in the SH3BP2 gene. Our aim is to report a case of a family of three siblings with cherubism and to discuss aspects regarding the clinical features of this disorder and its multidisciplinary management.

Materials and Methods:
Three siblings of different ages with bilateral enlargement of the jaws have been followed over the years by a multidisciplinary medical team.

Results:
The imagiologic study showed extensive multilocular and radiolucent lesions of the mandible and maxilla in the three patients. Upper airway obstruction and ocular involvement were excluded. The diagnosis of cherubism was confirmed by the demonstration of a SH3BP2 gene mutation in the genetic test. A conservative “wait and see” approach is being followed until the stabilization of the lesions. The oldest female patient underwent surgery due to functional and aesthetic concerns.

Conclusion:
The severity of the disease phenotype is highly variable, even within family members. Diagnosis is based on a combination of clinical signs, family history, radiographic findings and genetic testing. Because the most cases of cherubism are usually self-limiting and regress spontaneously after puberty, a longitudinal observation and follow-up is the initial management. Surgical procedures may be indicated for functional or aesthetic reasons and should be performed when the lesions become quiescent.

Sessão I
C09

Polyostotic fibrous dysplasia and the role of NaF PET/CT – A case report

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Introduction:
Fibrous Dysplasia (FD) is a mosaic progressive bone dysplasia caused by postzygotic gain-of-function mutations in the GNAS gene. It can affect one (monostotic) or multiple bones (polyostotic) leading to bone deformity, fractures and associated pain. FD can occur associated with extra skeletal manifestations, such as skin hyperpigmentation, hyperfunctioning endocrinopathies and precocious puberty (McCune-Albright syndrome). Bone scintigraphy is usually essential for diagnosis and staging, but recent studies have shown 18 NaF PET/CT to be superior, allowing for beNer quantification of disease activity.

Case report:
We report a case of an 11-year-old male with polyostotic FD affec)ng the pelvis, femurs, tibias, and small bones of the feet, previously submiNed to mutiple orthopedic surgeries due to several femoral fractures. Diagnosed at 4 years of age, this patient was recently referred to our center for thorough multidisciplinary assessment and follow-up. Patient underwent a18 FNaF PET-CT, the first time such exam was used for a bone dysplasia in our center and, to our knowledge, in Portugal.

Discussion:
Taking the present case as an example, we discuss the challenges on multidisciplinary assessments and follow-up in polyostotic FD taking into account the international guidelines for this condition. We highlight the importance of correct diagnosis and complete staging evaluatition for skeletal and extrasekeletal evaluation. In particular, we discuss the role of nuclear imaging (18 NaF PET/CT) in the monitoring of disease activity.

Keywords: Fibrous dysplasia; McCune-Albright syndrome; FD/MAS; polyostotic; NaF PET/CT.

Musculoskeletal Manifestations in Mucopolysaccharidoses: 38 Years Experience in a Orthopedic Department

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Serviço de Ortopedia Pediátrica do Hospital Pediátrico – CHUC, EPE

Background:
Mucopolysaccharidoses (MPS) are lysosomal overload diseases caused by progressive accumulation of glycosaminoglycans in various organs and tissues. This work aims to characterize the evolutionary musculoskeletal alterations in patients with MPS.

Methods:
Retrospective study of musculoskeletal changes, as well as the treatment performed (surgical or not) in patients with MPS followed from 1985 to 2022 in our center.

Results:
35 patients (18 male, 17 female) with MPS types I(10), II(3), III(9), IV(5), V(6) and VI(2) were included. Joint stiffness was present in 12 patients, 9 of which at the level of the fingers and/or knees; 1 patient underwent stretching of the hamstring and Achilles tendons. Four patients had valgus knees, 2 of which were treated surgically (temporary medial hemiepiphysiodesis of the femur and tibia in 1, varization osteotomy of the tibias in 1). Seven patients were diagnosed with carpal tunnel syndrome, 5 of which underwent surgical treatment. Regarding the spine, 4 patients had cervical stenosis and 7 hypoplasia of the odontoid (4 with atlantoaxial instability). Of these, 4 patients underwent cervical arthrodesis, with or without occipital extension, with or without canalar decompression. Twelve patients developed thoracolumbar kyphosis and 5 scoliosis. Of these, 5 wore a brace and 4 underwent surgical correction of kyphosis/scoliosis.

Conclusion:
The heterogeneous presentation of MPS and their broad spectrum of severity make their identification challenging. It's important alert the orthopedic community to the musculoskeletal manifestations of MPS, as aforementioned, for their early suspicion, referral, diagnosis and treatment.

Sessão II
C11

Multiple long bones fractures management in a case of Coats Plus Syndrome

Cláudio Garcia, Inês Balacó, João José Cabral, Maria Pia Monjardino, Cristina Alves

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Introduction:
Coats plus syndrome (CPS) is a rare multisystemic autosomal recessive disease that affects the eyes, brain, bone, and gastrointestinal system. Skeletal abnormalities, including generalized osteopenia, altered longitudinal growth, and metaphyseal abnormalities, have been previously reported in CPS patients.

Methods:
File revision

Results:
We present a 14-year-old girl diagnosed with Coats Plus Syndrome, with multiple long bone fractures. The patient also had skin hyperpigmentation, leukoplakia, and onychodystrophy (the classic mucocutaneous triad usually associated with dyskeratosis congenita), premature graying of the hair, bone marrow failure, hepatitis, exudative retinopathy and intracranial calcifications and brain cysts. Over the years, the patient presented fracture of right humerus (conservative treatment), right forearm fracture (closed reduction and elastic nailing), bilateral femur (closed reduction and femur nailing) and tibia fractures (conservative tratment). She developed bilateral knee valgus, inicially treated with bilateral tibia hemiepiphysiodesis, that did not succeed, and already was submitted to a left tibial tibial realignment osteotomy with a humerus nail.

Conclusion:
CPS is a rare disease that affects the bones with generalized osteopenia causing several long bones fractures. This case demonstrated the need to adapt surgical techniques to a patient with a specific phenotype. A multidisciplinary approach is mandatory in order to optimize medical and surgical treatment.

Genetic heterogeneity and diagnostic yield in a cohort of 101 patients tested for skeletal dysplasias

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Background:
Skeletal dysplasias (SD) encompass over 450 distinct clinical entities characterized by abnormal bone and connective tissue development. Due to their clinical and genetic heterogeneity, obtaining a molecular diagnosis is crucial for accurate classification of SD, essential for appropriate clinical care, effective management, and precise genetic counseling.

Methods:
At CGPP, we have implemented a whole-exome sequencing (WES)-based multigene panel, currently comprising 473 genes, with the aim of identifying the underlying genetic causes of SD.

Results:
Since 2016, we have tested 101 individuals with SD, including 51 fetuses. Out of the total, we successfully identified pathogenic or likely-pathogenic variants in 44 unrelated individuals (45.5% prenatally and 54.5% postnatally). Among these 44 individuals, 11 had previously described variants in the FGFR3 gene. Additionally, we discovered disease-causing variants in 20 other SD-related genes, including 11 novel variants not previously reported in the literature, in ASXL1, COL1A1, COL1A2, COL5A1, EBP, EVC, FBN1, OBSL1, PHEX, ROBO3, and TRAPPC2. Furthermore, we detected copy number variants affecting at least one SD-related gene in six individuals. In 32 patients, we reported variants of unknown clinical significance (VUS), requiring further investigation for variant reclassification, such as phenotype correlation, reverse phenotyping, familial variant segregation analysis, or functional studies.

Conclusion:
Our WES-based multigene panel for SD demonstrated a high diagnostic rate (44/101; 43.6%), reducing time-to-diagnosis and providing the opportunity for future reanalysis of inconclusive cases as new genotype-phenotype correlations and SD-related genes emerge

Sessão II
C13

The importance of a multidisciplinary approach in the assessment of Craniosynostosis – findings and lessons from a case series

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Introduction:
Craniosynostosis (CS) occurs in 1 per 2500 live births. Etiology is frequently multifactorial, with studies showing a genetic cause in around 20% of cases. Aiming to characterize patients diagnosed with CS at our center, we established a database (CRASY). We report our findings and propose a protocol for CS management.
Methodology: Descriptive analysis of primary CS cases, diagnosed between Jan 2011 and Jun 2022. We reviewed clinical files and set appointments when needed. Genetic testing ordered according to phenotype included Sanger sequencing for hotspot variants in FGFR2 (OMIM *176943) and FGFR3 (OMIM*134934) genes, WES-based NGS panel, and array-CGH.

Results:
A total of 45 patients were diagnosed with primary CS with 31 undergoing genetic investigation. An etiological diagnosis was achieved in 11 patients: three with Saethre-Chotzen Syndrome, two with FGFR2-related craniosynostosis, one with Apert Syndrome, one with Crouzon Syndrome, one with Muenke Syndrome, one with Greig Syndrome, one with Craniosynostosis 4, and one with TLK2-related Intellectual developmental disorder. In two cases the causative variant was inherited from an affected parent. 14 patients were referred to clinical genetics following the start of the CRASY registry.

Discussion:
An etiological genetic diagnosis was achieved in 24% of patients, allowing specific follow-up plans and genetic counseling of families. The majority of undiagnosed patients underwent investigation and parents received counseling with recurrence risks based on empiric evidence. Our protocol allowed for clear indications for diagnosis, genetic testing, and follow-up of patients in our center.

RPL13-related spondyloepimetaphyseal dysplasia – expanding the phenotypic spectrum

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In 2019, heterozygous variants in RPL13, encoding ribosomal protein L13 (component of the 60S subunit), which plays a crucial role in translation, were shown to cause a form of spondyloepimetaphyseal dysplasia (SEMD), initially described in 2013 (known as SEMD Isidor-Toutain type).

We recount eleven patients diagnosed in a multicenter consortium, from six different families, all carrying different RPL13 variants, located in the known hotspot region, of which five are novel. Six patients inherited the variant from an affected parent (6/10) and four were proven to be de novo (4/10). Clinically, 9/11 patients had short stature, all evaluated presented coxa vara, genu varum and vertebral anomalies, 8/8 had metaphyseal changes and delayed epiphyseal ossification, with 6/8 presenting metaphyseal “corner fractures” in childhood, a feature previously not described. Extraskeletal features such as myopia, iris coloboma and joint hypermobility were described in a singular fashion.

This presentation will focus on the evolution of three of the cases, a mother-son duo and a single de novo case, from two unrelated families of Portuguese origin, with long-term follow-up in CHUC (Coimbra). All three patients had severe short stature, platyspondyly and long bone deformities, namely genu varum, having been submitted to different surgical approaches in infancy. The mother, now in her 30’s, developed severe, painful coxarthrosis.

This cohort description doubles the number of SEMD-RPL13-related cases and variants reported to date. We intend to better characterize the phenotypic timeline, highlighting previously unreported age-related clinical and radiological features, promoting awareness of its natural history and growing phenotypic spectrum.

Sessão II
C15

A family with Spondyloepimetaphyseal Dysplasia, Type RPL13

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Spondyloepimetaphyseal Dysplasia (SEMD), Type RPL13 is an ultra-rare autosomal dominant primary bone dysplasia, caused by pathogenic variants in RPL13. We report a 27-year-old male patient, who was first referred at 14 years old with shorter stature (-1SD) and facial dysmorphic features (coarse facies, thick eyebrows and hair, deep-set eyes). Morquio Syndrome was first suspected, but excluded through normal biochemical assay and urine glycosaminoglycan levels.

Radiological findings suggested a skeletal dysplasia (showing levoconvex lumbar scoliosis, lumbar hyperlordosis, several dysmorphic dorso-lumbar vertebrae, dysmorphic proximal femoral epiphyses, irregular proximal tibial metaphyses and lower limb dysmetria). Currently, he also has an autoimmune disorder (primary Sjögren's syndrome). His father has a similar phenotype, with severe disproportionate short stature (~155cm, -3SD), with short trunk, scoliosis and flexed position of the knees and elbows. The genetic diagnostic pathway through array CGH (2013) and two NGS skeletal dysplasia panels (2015, 31 genes analysed; 2017, 419 genes analysed) did not find diagnostic pathogenic variants. The trio exome analysis (2022) detected a heterozygous missense probably pathogenic RPL13 variant: NM_000977.4:c.548G>A p.(Arg183His), inherited from his affected father.

This variant affects a highly conserved amino acid in the eL13 protein, component of the 60S ribosomal subunit. The same missense variant has been previously reported in one family with this diagnosis (PMID: 37121912). Our patient's radiological features and familial history correlate with the autosomal dominant SEMD Type RPL13 (#618728) diagnosis, previously known as Isidor-Toutain Type. To date, and to our knowledge, there are only twenty-five reported cases in literature.

Case report of metaphyseal (acro)scyphodysplasia – sequela of neonatal sepsis

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Introduction:
Acroscyphodysplasia (MIM: 250215) is a rare form of metaphyseal dysplasia characterized by distal femoral and proximal tibial (cone-shaped) epiphyses embedded in cup-shaped and large metaphyses known as metaphyseal scyphodeformity ("scypho" = cup). Affected individuals usually present severe short stature with micromelia, knee flexion and, often, brachydactyly. In the majority of the described cases, it is considered as a phenotypic variation of pseudohypoparathyroidism or acrodysostosis 2 with causative variants identified in either GNAS, PRKAR1A or PDE4D.

Case report:
We report a 4-year-old boy, born prematurely at 34 weeks of gestation and who had neonatal severe late-onset sepsis due to Klesiella pneumoniae. He latter developed global developmental delay, asymmetric ventriculomegaly with cortical atrophy and bilateral sensorineural profound hearing loss. At the age of 3, he had an episode of lower limb pain, which later improved. Radiographic studies at that time revealed striking bilateral metaphyseal scypho deformities at the knees, associated with milder bilateral upper femoral metaphyseal anomalies. No hand anomalies or dysmorphic features were noticed, and growth was normal. Skeletal dysplasia NGS multi-gene panel, including GNAS, PRKAR1A and PDE4D, was negative.

Discussion:
Among the few metaphyseal acroscyphodysplasia patients reported in the literature without a molecular diagnosis, it is noteworthy that medical records revealed early severe infection in two out of the three cases (Michot et al. 2018). Through contact with colleagues from other hospitals, several other unpublished similar cases are known. Despite further studies are needed, perinatal or infantile sepsis seems to be the major causative event in these cases. The proposed pathogenic mechanism for the skeletal phenotype is septic embolism of the epimetaphyseal perforating arteries.

Sessão II
C17

Roifman Syndrome: Case report of a rare multisystem bone dysplasia underlining challenges in differential diagnosis

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Introduction:
Biallelic pathogenic variants in RNU4ATAC gene cause RNU4atac-opathies with a spectrum of clinical phenotypes. Roifman syndrome (RS) is a distinct phenotype characterized by intrauterine growth restriction (IUGR), short stature, spondyloepiphyseal dysplasia, immunodeficiency, and developmental delay (DD)/intellectual disability. Additional features include mild microcephaly, facial dysmorphism, brain, cardiac, and renal malformations, deafness, and eye abnormalities.

Case report:
A 4-year-old boy, born prematurely to non-consanguineous parents, presented with late IUGR, DD, short stature, relative macrocephaly, facial dysmorphism (brachycephaly, frontal bossing, low-set posteriorly rotated ears, hypertelorism, downslanted palpebral fissures, full cheeks, anteverted nares, brachydactyly, fifth finger clinodactyly, fetal finger pads, deep palmar and plantar creases), and recurrent otitis media in the first year of life. Bone X-rays showed delayed bone age, vertebral beaking, and bilateral femoral bowing. ArrayCGH and urine glycosaminoglycan (GAG) analysis were normal. Urine oligosaccharide analysis suggested Fucosidosis, but enzyme activity in leukocytes and FUCA1 gene sequencing were both normal. Subsequent WES analysis identified two heterozygous variants in RNU4ATAC gene: n.13C>T and n.48G>A, classified as pathogenic and likely pathogenic, respectively. Segregation analysis is still ongoing.

Discussion:
Urine analysis of GAG and oligosaccharides can delay diagnosis in low pre-test clinical suspicion cases. WES is essential for identifying rare multisystem bone dysplasia syndromes and enables improved follow-up. In our patient, RS diagnosis guided personalized and multidisciplinary management, including ophthalmological, cardiac, and immunological surveillance, and provided accurate genetic counselling to the family.

"Erlenmeyer flask sign", a clue to explore further

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The "Erlenmeyer flask sign" is a non-specific radiographic finding seen in certain genetic disorders, such as Gaucher disease, Mucopolysaccharidoses and skeletal dysplasias. It appears as a widened metaphysis of the long bones, resemblant to an "Erlenmeyer flask" shaped appearance on X-rays. Here we present a 41-year-old male referred to our genetic appointment due to the presence of the "Erlenmeyer flask sign" on a radiograph of the right knee taken afterwards a sports injury. From his personal history, he was submitted to four osteotomies of the facial bones due to bone overgrowth.

No relevant family history or parental consanguinity are known. At genetic evaluation, he had a craniofacial characteristic appearance, with wide-set eyes, narrow nasal root, and prominent forehead. Lower limbs radiograph showed an increase in the cross-sectional diameter of the long bones with marked elongation of the metaphysis. Electrocardiogram, echocardiogram, abdominal ultrasound, and blood analyses liver function were normal. Due to the clinical suspicion of Craniometaphyseal dysplasia, a genetic targeted analysis was performed, enabling us to identify a pathogenic variant, in apparent homozygousity in the GJA1 gene. This variant had previously been described in homozygosity in another Portuguese patient with Craniometaphyseal dysplasia, thus supporting the autosomal recessive mode of inheritance of this disease (PMID: 23951358). To sum up, this case reinforces the importance of integrating clinical and radiological findings when discussing differential diagnoses, allowing to direct the genetic study.

Sessão II
C19

Prenatal presentation of TBX6-associated vertebral malformations

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Spondylocostal dysostosis (SCD) comprises a group of skeletal dysplasias characterized by multiple segmental defects involving vertebra and ribs.

We present the case of a 34-year-old woman, gravida II para I (daughter with phenylketonuria), with no relevant medical history and a non-consanguineous partner. The ultrasound performed at 22 weeks of gestation revealed lumbar spine anomalies and scoliosis resulting from at least two hemivertebrae, without additional anomalies. Subsequent fetal CT confirmed the scoliosis along with vertebral segmentation defects (butterfly vertebra and hemivertebrae), and delayed development of the 12th left rib. The couple decided to terminate the pregnancy, and post-mortem examination confirmed the prenatal findings and identified also cervical ribs.

Cytogenetic analysis (aCGH) was normal. Further investigation using a NGS panel identified a likely pathogenic heterozygous variant in TBX6, inherited from the asymptomatic mother.

Most of the previously reported TBX6-associated vertebral malformations exhibit autosomal recessive inheritance, requiring two pathogenic variants or a loss-of-function variant and a hypomorphic haplotype (consisting of three specific polymorphisms) in trans configuration. A single family has been described with an autosomal dominant SCD. The phenotypic spectrum ranges from congenital scoliosis to SCD, depending on the extent of TBX6 loss-of-function.

In our family, the reported haplotype was absent in the fetus, leading to the hypothesis of a second undetected deleterious variant or an unrecognized hypomorphic allele, contributing to the vertebral segmental defects in the fetus but not in the mother. This underscores the significance of genetic counselling and highlights the need for further studies to unravel TBX6 pathogenicity and its associated implications

SPONDYLOCARPOTARSAL SYNOSTOSIS SYNDROME – CLINICAL CASE

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Introduction:
Spondylocarpotarsal synostosis syndrome (SCT) is a very rare genetic disease caused by a mutation in the Filamin B gene, giving rise to a skeletal dysplasia characterized by vertebral segmentation defects. Apart from severe vertebral defects, the disease is associated with carpal and tarsal synostosis which is quite characteristic for the disease.

Methods:
Clinical case of a 4-year-old child, referred to Orthopedics for scoliosis. Due to associated short stature, she was referred to Genetics and the diagnosis was suspected based on radiological evaluation (scoliosis and carpal-tarsal synostosis) and confirmed by molecular study. During the past 12 years, she underwent 3 spinal surgeries. The SYQoLQ score was applied.

Results:
The molecular study identified a homozygous mutation in the FLNB gene - c.7190delG. In this context, at 5 years of age, an anterior T7 -T11 arthrodesis by anterolateral thoracostomy was performed for a congenital scoliosis of left convexity with progressive lordosis caused by a T6-T11 posterior fusion. At age 8, because of progressive scoliosis, she underwent stretching with halofemoral traction for 68 days, followed by placement of magnetic controlled growing rods. At last, at 16 years of age, she was graduated with a definitive T2-L4 posterior arthrodesis. Three months after graduation surgery, she presents a SYQoLQ score of 49.

Conclusion:
Children with scoliosis and short stature should consider the possibility of SCT. Knowledge of this disease is essential for early identification and treatment, important in obtaining good therapeutic results.

Sessão II
C21

POLYOSTOTIC FIBROUS DYSPLASIA – CLINICAL CASE

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Introduction:
Fibrous Dysplasia is an uncommon disorder of the bone caused by mutations of the Gsα protein encoded by gene GNAS, in which bone is replaced by fibro-osseous tissue. The disease may be monostotic or polyostotic (PFD).

Methods:
A case report of a 4-year-old male child diagnosed with polyostotic fibrous dysplasia who initially presented a pathological fracture of the right proximal femur, treated conservatively. After it, a series of complications followed during growth, requiring several surgical interventions. At 14-year of follow-up, Kidscreen10 score was applied.

Results:
After multiple fractures and persistence of the shepherd's crook deformity of the right proximal femur, he underwent a valgus osteotomy at the age of 5 years. Multiple complications occurred during, including bone deformities requiring surgical intervention, peri-implant fractures, failure of various osteosynthesis constructions, and progression of deformities requiring new osteotomies. At 11 years of age, cephalomedullary femoral nailing of the right femur and definitive percutaneous epiphysiodesis of the contralateral distal femur were performed. At 12 years of age, he suffered a fracture of the proximal tibial shaft treated with a tibia nail. Multiple fractures of the humerus and forearm were documented, in the context of minor trauma, treated conservatively. At the end of skeletal maturity, he presents with significant lower limb dysmetria (asymmetry of 8 cm). At 18 years of age, despite the dysmetria, he presents a Kidscreen10 score of 42/50.

Conclusion:
PFD is a heterogeneous disease that requires a multidisciplinary approach. Surgical treatment is challenging, requiring multiple episodes of reconstructive surgery throughout growth

Sleep apnea and cervicomedullary decompression in Achondroplasia

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Introduction:
Respiratory sleep problems are common in children with achondroplasia, particularly obstructive sleep apnea (OSA). Brain stem compression and airway muscle hypotonia, by foramen magnum stenosis, play an important role in both central and obstructive respiratory disturbances.

Case report:
Boy with achondroplasia, now with 2years, was first observed in a Pneumology consultation at 1,5months. Parents report a noisy breathing and intermittent irregular breathing during sleep. Polysomnography (PSG) at 2months revealed moderate OSA – no snoring, obstructive apnea-hypopnea index (AHI) 8,8/h, a central apnea index of 1/h, minimum SpO2 87% and desaturation index of 3,4/h. Non-invasive ventilation (NIV) during sleep was started with good tolerance. At 4months of age, because of significant foramen magnum stenosis and pyramidal signs on neurological examination, he was submitted to cervicomedullary decompression. Two months later he began to refuse NIV. PSG at 13months revealed a mild OSA - no snoring, obstructive AHI of 1,1/h, a central apnea index of 0/h, minimum SpO2 94% and a desaturation index of 0.8/h. Adenotonsillectomy was performed at 19months because of frequent upper airway infections and clinical OSA, with clinical resolution.

Conclusion:
Polysomnography is essential in respiratory characterization in the first months, even without snoring. Obstructive sleep apnea can be related to foramen magnum stenosis and improve after cervicomedullary decompression.

Sessão III
C23

Importance of polysomnography in Achondroplasia management

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Introduction:
Polysomnography (PSG) is the gold standard for the diagnosis of obstructive sleep apnea syndrome (OSAS) in achondroplasia. This exam is indicated even in the absence of respiratory symptoms and after ENT procedure.

Case report:
Girl with achondroplasia, now 6years old, was first observed in a Pneumology consultation at 4months. Parents report occasional noisy breathing during sleep but no snoring. PSG at 9months revealed severe OSAS – intermittent snoring, obstructive apnea-hypopnea index (AHI) 14/h, a central apnea index of 1.1/h, minimum SpO2 76%. Brain MRI showed mild foramen magnum stenosis. Non-invasive ventilation (NIV) during sleep was started with good tolerance. Snoring and restless legs when NIV was not used was reported during follow-up. Adenotonsillectomy was performed at 4years due to multiple upper respiratory infections and conductive hearing loss. After ENT procedure, parents stopped NIV and once again just noisy breathing was report. PSG showed severe OSAS–snoring, obstructive AHI 14.8/h, a central apnea index of 0/h, minimum SpO2 78%. NIV was restarted with success.

Conclusion:
Severe OSAS can be present even without symptoms. PSG is essential in achondroplasia management.

Poster 01

Implicações sociais associadas às Displasias Ósseas
Social implications associated with Bone Dysplasias

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Resumo:
O presente artigo compreende a atividade de pesquisa no âmbito da unidade curricular Estágio II, que integra o sétimo semestre (4.º ano) de Licenciatura em Serviço Social, na Faculdade de Psicologia e Ciências da Educação da Universidade de Coimbra. Esta investigação procurou compreender as implicações individuais, familiares e sociais das crianças e jovens com Displasia Óssea, uma condição óssea rara com caraterísticas físicas evidentes. Desta forma, os resultados deste estudo exploratório vêm demonstrar a importância do conhecimento sobre doenças e condições raras, fundamental ao nível dos cuidados clínicos e especializados, mas, também, ao nível individual, familiar e social, na medida em que um indivíduo, ao deter de informação fundamentada e fidedigna acerca da doença e dos seus direitos, tem o poder de alterar comportamentos e desmistificar conceitos e preconceitos, fundamental para o aumento da qualidade de vida, destacando-se o papel das associações de apoio, como a Associação Nacional de Displasias Ósseas (ANDO), e do Serviço Social.
Palavras-chave: Displasias Ósseas. Implicações sociais. ANDO. Apoio social.

Abstract:
This article comprises the research activity within the scope of the Internship II curricular unit, which is part of the seventh semester (4th year) of the Degree in Social Work, at the Faculty of Psychology and Educational Sciences of the University of Coimbra. This investigation sought to understand the individual, family and social implications of children and young people with Osseous Dysplasia, a rare bone condition with obvious physical characteristics. In this way, the results of this exploratory study demonstrate the importance of knowledge about rare diseases and conditions, fundamental at the level of clinical and specialized care, but also at the individual, family and social level, insofar as an individual, when detaining of grounded and reliable information about the disease and its rights, has the power to change behaviors and demystify concepts and prejudices, fundamental for increasing the quality of life, highlighting the role of support associations, such as the National Association of Dysplasias Bone (ANDO), and Social Work.
Keywords: Bone Dysplasias. Social implications. ANDO. Social support.