5as JORNADAS DE DOENÇAS ÓSSEAS RARAS

Coimbra, 30 de junho e 1 de julho de 2025

ISEC › Instituto Superior de Engenharia de Coimbra

5th Meeting on Rare Bone Diseases

Coimbra, 30th June and 01st July 2025

LIVRO DE RESUMOS

Organização / Organization:

- Equipa Multidisciplinar de Doenças Ósseas Raras da Unidade Local de Saúde de Coimbra (ULS Coimbra-ERN-BOND)
- **GruPEDGE**
- Associação de Saúde Infantil de Coimbra

5as Jornadas de Doenças Ósseas Raras de Coimbra

5th Coimbra's Meeting on Rare Bone Diseases

15:10-16:10 Comunicações orais - Casuísticas e Casos Clínicos I / *Oral communications - Clinical Cases I* (PT/EN)
Moderação / *Moderation*: Maria Pia Monjardino, HP-ULS Coimbra, André Travessa, ULS Santa Maria

***I.1. Clinical and Phenotypic Characterization of Fibrous Dysplasia Patients in a Portuguese Multidisciplinary Rare Bone Diseases Clinic* (8'+2')**

Maria João Cadório, ULS Coimbra

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Ana Sofia Correia, ICBAS

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Mafalda Gonçalves ULS Coimbra

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Joana Azevedo Silva, ULS Trás-os-Montes e Alto Douro

I.1. Clinical and Phenotypic Characterization of Fibrous Dysplasia Patients in a Portuguese Multidisciplinary Rare Bone Diseases Clinic *(8'+2')*

Maria João Cadório[1], Camila Sousa[1], Sara Alves Costa[1], Mariana Rodrigues[1], Fabiana Gouveia[1], André Saraiva[1].

[1] *Serviço de Reumatologia, Unidade Local de Saúde de Coimbra*

Introduction: Fibrous dysplasia (FD) is a rare, non-hereditary bone disorder where normal bone is replaced by fibro-osseous tissue. It may be monostotic, polyostotic, or part of McCune-Albright Syndrome (MAS) when associated with endocrine and cutaneous involvement.[1] We aimed to characterize patients with FD followed in a multidisciplinary rare bone disease clinic at a Portuguese center.

Methods: Retrospective descriptive study of FD patients under follow-up at a tertiary Rheumatology Department. Clinical data were obtained from medical records and analyzed using descriptive statistics.

Results: Fourteen patients were included (57.1% female; mainly Caucasian (85.7%) median age 26.0; median age at diagnosis 10.0). FD was polyostotic in 78.6%, MAS in 72.7% of those. Presenting features included bone pain (35.7%), fractures (21.4%), deformity/swelling (14.3%), precocious puberty (14.3%). Diagnosis was incidental in 21.4% of the cases. Bone deformities occurred in 78.6%, with craniofacial involvement in 64.3%, and Shepherd's crook deformity in 21.4%. Fractures (42.9%) mostly affected femur, tibia, humerus, and pelvis. Short stature was present in 21.4%. Bone biopsy was performed in 35.7%; GNAS testing in 21.4% (1 compatible). Endocrinopathies occurred in 50%, including precocious puberty, acromegaly, Cushing's, and hyperprolactinemia. Neurological complications, mainly optic nerve compression, affected 28.6%, and café-au-lait spots 42.9%. Treatments included bisphosphonates (57.1%), hormonal therapy (35.7%), and surgery (42.9%).

Conclusion: This series highlights the clinical heterogeneity of FD/MAS and reinforces the importance of early diagnosis and multidisciplinary care; genetic testing may aid diagnosis in selected cases. Our experience helps fill a gap in literature, largely pediatric-focused, and supports the need for collaborative registries in adult FD/MAS populations.

References: Spencer T, Pan KS, Collins MT, Boyce AM. The Clinical Spectrum of McCune- Albright Syndrome and Its Management. Horm Res Paediatr. 2019;92(6):347–56.

I.2 TRPV4 skeletal disorders: assessment of phenotypic spectrum and impact on quality of life of Portuguese patients *(8'+2')*

Ana Sofia Correia; Cláudia Falcão Reis; João Freixo; André Travessa; Sérgio Sousa; Carolina Lemos

ICBAS; ULS Santo António; ULS Coimbra; ULS Santa Maria

Background: Mutations in the transient receptor potential cation channel vanilloid 4 (TRPV4) are linked to a spectrum of skeletal dysplasias, from severe metatropic dysplasia (MD) to milder autosomal dominant brachyolmia (ADB), significantly impacting patient quality of life (QoL).

Objectives: This study aimed to characterize Portuguese patients with TRPV4-related skeletal disorders, infer genotype-phenotype correlations, and assess QoL.

Methods: A retrospective analysis of 12 patients with TRPV4-related bone dysplasia from three Portuguese hospitals was conducted, collecting demographic, clinical, and genetic data. QoL was evaluated using the EQ-5D questionnaire.

Results: We evaluated 12 patients (58.3% female; median age 15 years) from 9 families. Half had MD, mainly linked to the recurrent p.Pro799Leu variant, with others having p.Pro799Ala and p.Glu797Lys. Spondylo-metaphyseal dysplasia Kozlowski type (SMDK) was found in three patients with the p.Arg594His variant. A novel p.Gly595Glu variant was identified in three family members with an intermediate phenotype between ADB and spondylo-epiphyseal dysplasia Maroteaux type (SEDM). Common features included kyphosis, platyspondyly, and epiphyseal dysplasia. All patients had a height z-score ≤−2 at last assessment. The median diagnosis age was 78 months, with a notable referral-to-diagnosis delay. QoL scores showed varying impacts, with self-care and usual activities often presenting fewer problems.

Conclusion: Our study reinforces the link between MD and SMDK with specific mutations in exons 15 and 11, respectively, confirming p.Pro799 and p.Arg594 as frequent mutation hotspots. It highlights MD's more severe presentation and emphasizes the need for continued research into new TRPV4 variants and multidisciplinary clinical management to improve QoL for affected individuals.

I.3 Multiple Osteochondromas: Clinical and Molecular Characterization of a Portuguese cohort *(8'+2')*

Ana Mafalda Gonçalves[1], Sofia Fernandes[1], Emanuel Homem[2], Inês Balacó[2], Cristina Alves[2], Maria Pia[2], Célia Nogueira[3], Altina Lopes[3], Cristina Pereira[3], Laura Vilarinho[3], Karen Heath[4,5], Luisa Diogo[6], Sérgio B Sousa[1,7]

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7 CIBERER, ISCIII, Madrid, Spain,

Multiple Osteochondromas (MO) is a rare genetic condition of autossomal dominant transmittion characterized by benign tumours emerging from the perichondrium of bones. It is a potentially debilitating disease, causing deformities, functional limitation and joint pain at multiple sites. A timely diagnosis of families at risk can enable early follow-up and management of complications, as well as preventing future cases. This study aims to provide a detailed clinical and molecular characterization of a group of patients referred for MO, thus expanding the knowledge about the variants most frequently associated with these phenotypes.

We performed a retrospective analysis of clinical features and genomic findings of a group of patients referred for multiple exostoses, with or without a positive family history. Patients with insufficient clinical records and no genetic testing were excluded from this group.

A total of 118 cases were analysed, across 81 families, 61 (51.7%) females and 57 (48.3%) males, with a mean age of 26.9 ± 15.5 years. A total of 89 (75.4%) patients were heterozygous for pathogenic or likely pathogenic variants involving *EXT1* or *EXT2* and five (4.2%) were heterozygous for variants of unknown significance involving *EXT1.* Of the remaining 24 (20.3%), 16 opted out of genetic testing, 6 had normal results on genetic testing and 2 had patogenic variants in a metochondromatosis-associated gene (PTPN11). These PTPN11 variants and two large deletions involving EXT1 and EXT2 were identified through new generation sequencing (NGS) after a negative sanger sequencing test. 92 cases presented enough clinical data to be classified according to Istituto Ortopedico Rizzoli. Of these, 26 (28.3%) placed in class IA/IB, 39 (42.4%) in class IIA/IIB and 27 (29.3%) in class IIIA/IIIB.

We observed that 77.1% of cases in this cohort had at least one causal variant, demonstrating a high diagnostic yield. However, the results suggest some additional benefit in using NGS as first line of diagnosis. With these results, we hope to contribute to a better understanding of the clinical aspects of the disease and to a more streamlined approach to diagnosing MO.

I.4. Identification of a novel *COL3A1* variant potentially underlying a mild vEDS phenotype across three generations *(5'+1')*

Diogo Fernandes da Rocha, MD*[1]; Pedro Louro, MD[1,2]

1: Serviço de Genética Humana, Hospital Universitário de São João, Unidade Local de Saúde de São João, Porto, Portugal; 2: Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal.

Background: Vascular Ehlers-Danlos syndrome (vEDS) is a rare connective tissue disorder typically caused by pathogenic variants in *COL3A1*, with clinical manifestations including arterial rupture, organ rupture, and distinct craniofacial features. However, phenotypic variability exists, particularly in association with variants located in the terminal regions of the protein (PMID: 25758994).

Methods: We evaluated a 66-year-old woman referred for acroosteolysis of the distal phalanges of the right hand, alongside short stature and early tooth loss. Comprehensive clinical assessment and genetic testing via clinical exome sequencing were performed. Segregation analysis was subsequently conducted in affected family members.

Results: A novel heterozygous missense variant in *COL3A1* [c.4109A>G, p.(Tyr1370Cys)] was identified in the proband. Despite the absence of major vascular complications or organ rupture, the patient displayed craniofacial features suggestive of vEDS, including a thin upper lip, micrognathia, and acrogeria. Segregation analysis confirmed the presence of the same variant in her daughter and granddaughter, who exhibited similar but mild phenotypic traits. No major complications have been observed in any affected individuals to date.

Conclusion: The clinical and genetic findings suggest that the *COL3A1* c.4109A>G variant may underlie the phenotype observed in this family. Given its location in the C-terminal region and the mild clinical course, this variant may represent a less severe form of vEDS. In view of the substantial psychological and clinical implications of a vEDS diagnosis, a cautious interpretation is warranted. Further functional characterization and longitudinal follow-up are necessary to clarify pathogenicity

I.5. Nail–Patella Syndrome Beyond the Skeleton: Highlighting Vascular Complications *(5'+1')*

Mariana Mendes Rodrigues[1], Fabiana Gouveia[1], Sara Costa[1], Maria João Cadório[1], Camila Sousa[1], André Saraiva[1]

1- Rheumathology Service, Unidade Local de Saúde (ULS) de Coimbra

Nail–patella syndrome (NPS) is a rare autosomal dominant disorder caused by pathogenic variants in the *LMX1B* gene. It typically presents with nail dysplasia, hypoplastic or absent patellae, iliac horns and elbow abnormalities. The syndrome results from altered transcription of genes involved in limb, renal and ocular development, and may affect extracellular matrix proteins such as collagen types I and III.

We present the case of a 37-year-old woman with chronic joint pain, functional limitation, nail abnormalities, and iliac horns on radiography. Genetic testing confirmed NPS with a pathogenic *LMX1B* variant. Her medical history includes asthma, allergic rhinitis, extrasystoles, and notably, a hemorrhagic stroke in the left thalamo-capsular region, extending into the lateral ventricle, causing tetraventricular hemorrhage. This resulted in gait imbalance, mild right hemiparesis, sensory and proprioceptive deficits, and mild bilateral fourth cranial nerve paresis. Extensive workup found no clear etiology.

Literature on vascular anomalies in NPS is scarce but includes reports of internal carotid artery aplasia, spontaneous coronary artery dissection, and ST-elevation myocardial infarction with anomalous coronary anatomy and aneurysms. This case raises the possibility of vascular involvement in NPS, supporting the hypothesis that *LMX1B* mutations may impair endothelial development or vascular integrity, considering the role of Type I and III collagen in vascular walls.

We emphasize the importance of recognizing non-musculoskeletal complications in NPS, particularly vascular events. Further research is needed to clarify whether these are coincidental findings or inherent to the disease. Multidisciplinary follow-up is essential to address its full clinical spectrum.

I.6 Rehabilitation in Pycnodysostosis: A Multidisciplinary Approach to Improving Clinical and Mental Outcomes *(5'+1')*

Cláudia Aguiar[1,2], Tiago Teófilo[1], Énio Pestana[1], Pedro Silva[1], Inês Alves[2,3]

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2. ANDO Portugal
3. School of Health and Human Development, Évora University -CHRC, Évora, Portugal

Introduction: Pycnodysostosis (PYCD) is an ultra-rare skeletal dysplasia (1-5/ 1.000.000 births) characterized by bone fragility and reduced exercise tolerance (1). Individuals with rare diseases face significant mental health challenges and social isolation (2) with over 90% of experiencing anxiety and depression (3). Despite recommendations for comprehensive care, standardize rehabilitation and support protocols remain absent for this population (4).

Objective: To evaluate integrated multidisciplinary healthcare effects on clinical and mental health outcomes in an adult with genetically confirmed pycnodysostosis.

Methods: A 42-year-old woman with confirmed CTSK gene mutation underwent a tailored cardiorespiratory rehabilitation program (twice-weekly for 12 weeks) post-tibial fracture. Sessions included aerobic training, strength exercises, balance work and experience sharing. Assessments included functional capacity (6-minute walk test, Timed Up-and-Go test), psychological status (PHQ-9 and HADS), quality of life (SF-36) and physical activity (IPAQ). Sessions followed FITT-CORRECT prescription principles with individualized progression.

Results: Significant improvements were observed with 168.5% increase in walking distance (183m to 491.5m), 50% fall risk reduction (18s to 9s in TUG), and marked SF-36 improvements, particularly mental health (0 to 40 points) and emotional role (0 to 25 points). Depression decreased from moderate to minimal levels (PHQ-9: 10 to 4 points), anxiety reduced (HADS: 10 to 6 points) and exercise duration increased 51.6% (treadmill) and 400% (cycle ergometer), with decreased perceived exertion

Conclusions: This case demonstrates the feasibility and comprehensive benefits of tailored rehabilitation in Pycnodysostosis, achieving clinical, mental and psychosocial improvements. Findings highlight multidisciplinary approaches importance in optimizing outcomes in this vulnerable population.

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I.7 A Very Mild Form of Mohr Syndrome *(5'+1')*

Pavlina Rayko, Pedro Louro

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NIMA-related kinases (NEKs), such as NEK1, belong to the family of serine/threonine kinases that are thought to function in cell cycle control and cilia regulation. It has been proposed that NEK1 has functions in DNA double-strand repair, neuronal development, and ciliogenesis. Pathogenic variants in gene NEK1 were initially associated with Short-rib thoracic dysplasia-6 with or without polydactyly (SRTD6; MIM#263520), a potentially lethal skeletal ciliopathy. More recently, variants in this gene were associated with Orofaciodigital syndrome II (OFD2; MIM#252100), also known as Mohr syndrome. Main clinical features include short stature, conductive hearing loss, cleft lip/palate, dental anomalies, pectus excavatum, scoliosis, and poly-, syn-, and brachydactyly.

We report a 15-years-old male patient first referred to our consult at the age of 10 due to dental alterations (supernumerary teeth, taurodontism, claw cusps), myopia and astigmatism. He had normal psychomotor development and growth (weight P50-75, height P25-50, HC P50). He had thick eyebrows, thin upper lip, widely spaced nipples, pectus excavatum, small hands and feet, unilateral single transverse palmar crease, clinodactyly of the fifth fingers, sandal gap, and large first toe. Skeletal X-ray shows a slight reduction in the height of the vertebral bodies from D10 to D12. ENT evaluation at the age of 14 was normal.

Dental Anomalies NGS Panel revealed a homozygous probably pathogenic variant NM_012224.4:c.1226G>A p.(Trp409*) in gene NEK1. This variant was reported in compound heterozygosity with another probably pathogenic variant in two siblings with a OFD2 compatible phenotype, mild compared with the previously described lethal cases with NEK1 variants.

I.8 Hypophosphatasia in an Adolescent with Short Stature: A Case Report *(5'+1')*

Joana Azevedo Silva[1], Ana Rita A. Costa[2], Céu Mota[3], Maria Abreu[3], Teresa Borges[4], Catarina Mendes[4]

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Introduction: Hypophosphatasia (HPP) is a rare inherited skeletal disorder caused by *ALPL* gene mutations, resulting in deficient serum and bone alkaline phosphatase (ALP) activity and impaired bone and dental mineralization. Clinical manifestations range from a lethal perinatal form to mild adult phenotypes. In addition to skeletal involvement, seizures may occur.

Case Description: A 16-year-old girl with epilepsy and intellectual disability was referred to our multidisciplinary rare bone disease team. Prenatal history included fetal growth restriction. Postnatally, her weight tracked near the 10th percentile and height remained below the 3rd percentile, with growth arrest from age 12. Previous endocrine workup for short stature was unremarkable. Menarche occurred at 11. At age 12, radiographic assessment revealed advanced bone age. Physical examination revealed severe short stature, increased upper-to-lower segment ratio, and enamel defects. Genetic testing identified a heterozygous pathogenic variant in *ALPL* (c.1426G>A; p.(Glu476Lys)), inherited from her father. Two additional heterozygous missense variants of uncertain significance (VUS) were identified in *ACAN* and *PHEX* genes. Biochemical evaluation showed low serum and bone ALP levels.

Discussion: This case illustrates an atypical presentation of HPP with early growth arrest. Diagnosis was established based on clinical, biochemical, and genetic findings. Early recognition is essential for multidisciplinary management, including symptomatic treatment, dental and orthopedic care, and genetic counseling. Enzyme replacement therapy may be indicated in severe cases. The coexistence of short stature and epilepsy should raise a suspicion for HPP. In this patient, a second diagnosis should be suspected as advanced bone age is not typically associated with HPP.

08:40-10:00 Comunicações orais - Casuísticas e Casos Clínicos II / *Oral communications - Clinical Cases II* (PT/EN)
Moderação / *Moderation*: Renata d'Oliveira, ULS São João, Daniela Pinto, ULS São João

***II.1 Skeletal Dysplasias and the role of Growth Hormone – experience of a tertiary Pediatric Center* (8'+2')**

Ana Rita A. Costa, ULS Tondela-Viseu

***II.2 Osteogenesis Imperfecta: From Individuality to Multidisciplinarity- A Retrospective Study* (8'+2')**

Sara Alves Costa, ULS Coimbra

II.3 Natural history of thoracolumbar kyphosis in achondroplasia: a contribution from a reference center (8'+2')

Maria Pia Monjardino, ULS Coimbra

II.4 Clinical and molecular characterization of 17 patients with acrodisostosis and genotype -phenotype correlation (8'+2')

André Abreu, FMUL

II.5 Familial short stature and brachydactyly - PRKAR1A Variant of Uncertain Significance (5'+1')

Raquel Calheiros, IPO Porto

II.6. Epiphyseal Dysplasia with Sideroblastic Anemia: a mild presentation of EVEN-plus, or an entirely new entity? (5'+1')

Diana Macedo Cardoso, ULS de Santos António

II.7 Hajdu-Cheney syndrome: a familial case with possible new findings (5'+1')

Katerine Torres, ULS Santa Maria

II.8 COL27A1 Variants in a Child with Severe Scoliosis (5'+1')

Joana da Silva Cardoso, ULS São João

II.9 Bone Cysts in Juvenile Paget's Disease: Atypical Manifestation or Incidental Finding? (5'+1')

Fabiana Gouveia, ULS Coimbra

II.1 Skeletal Dysplasias and the role of Growth Hormone – experience of a tertiary Pediatric Center *(8'+2')*

Ana Rita A. Costa[1], Helena Ferreira[2], Joana Azevedo Silva[3], Maria Abreu[4], Cláudia F. Reis[4], Catarina Mendes[5], Joana Freitas[5], Maria João Oliveira[5], Teresa Borges[5]

[1]Unidade Local de Saúde (ULS) Tondela-Viseu, [2]Centro Materno Infantil do Norte (CMIN) - ULS Santo António, [3]ULS Trás-os-Montes e Alto Douro, [4]Centro de Genética Médica Doutor Jacinto Magalhães, CMIN - ULS Santo António, [5]Unidade de Endocrinologia Pediátrica, CMIN - ULS Santo António

Introduction Recombinant human growth hormone (rGH) is the first-line therapy in GH deficiency and small for gestational age (SGA) with failure to catch-up; however, its value in most skeletal dysplasias (SD) remains controversial.

Methods Anthropometric data from patients with SD receiving rGH in the Pediatric Endocrinology clinic of a tertiary-level hospital were collected and analyzed using Excel®, IBM SPSS Statistics®, and Anthro-Calc®. Non-normally distributed variables are reported as median with 25th and 75th percentiles.

Results Seven patients were included (71.4% male): four with SHOX-related syndromes, one with *GNAS*-associated SD, one with Cornelia de Lange syndrome, and one acrodysostosis. Median age at dysplasia diagnosis was 8.6 years (3.66; 11.89), and 10.1 years (7.33; 13.37) at rGH initiation. The Cornelia de Lange patient had GH deficiency; two patients were initially treated as SGA and subsequently diagnosed as SD. At the last assessment, median treatment duration was 1.2 years (0.9; 2.7), six patients remained on therapy (one temporarily lost follow up and stopped treatment) and no adverse reactions were reported. Baseline height z-score was -2.53 (-3.61; -2.44; minimum -6.25). All but one patient (the one that lost follow up) improved their final height z-score, with a median increase of 0.34 (0,07; 0,74). There was a general approximation toward mid-parental target height as well.

Conclusion rGH appears to be a safe therapeutic tool in SD, even in sever short stature. We highlight that SD may coexist with GH deficiency, and SGA without catch-up growth may harbor an underlying dysplasia.

II.2 Osteogenesis Imperfecta: From Individuality to Multidisciplinarity - A Retrospective Study *(8'+2')*

Sara Alves Costa[1], Mariana Mendes Rodrigues[1], Maria João Cadório[1], Fabiana Gouveia[1], Camila Sousa[1], André Saraiva[1]

1 - Rheumatology Department, ULS Coimbra

Introduction: Osteogenesis Imperfecta (OI) is a rare connective tissue disorder characterised by bone fragility and multisystemic manifestations. This study describes the clinical, demographic and therapeutic approaches of patients with OI in a dedicated Rare Bone Diseases Clinic.

Methods: We conducted a retrospective review of adult patients with a confirmed diagnosis of OI followed at the Rheumatology Department. Demographic data, clinical manifestations, functional status, complications and therapies were collected.

Results: Thirteen patients were included, 54% (n = 7) were female, with a mean age of 43 ± 12.1 years. Most patients (n = 8; 61.5%) were classified as having type I OI, with three patients (23.1%) having type III and two (15.4%) type IV. All patients initially presented with fractures, and short stature was reported in six cases (46.2%). The most frequent location of fractures was the lower or upper limbs (n=12, 92.3%). Genetic testing was performed in ten patients, all of whom carried variants in the COL1A1 gene. The most common extra-skeletal feature was blue sclerae (n = 11; 84.6%), followed by hearing loss (n = 6; 46.2%). Chronic pain was reported in eight patients (61.5%), and four (30.8%) required mobility aids. 84.6% of the patients had multidisciplinary follow-up, mainly with Rehabilitation and Otorhinolaryngology. Eight patients (61.5%) received bisphosphonate in adulthood, four zoledronate and the other four alendronate.

Conclusion: This study highlights the clinical heterogeneity of OI. Multidisciplinary long-term follow-up is essential to address the persistent skeletal and functional burden of the disease.

II.3 Natural history of thoracolumbar kyphosis in achondroplasia: a contribution from a reference center *(8'+2')*

Maria Pia Monjardino, , Sérgio Sousa, Alice Mirante, João Cabral, Pedro Cardoso, Emanuel Homem Costa, Marcos Carvalho, Oliana Madeira, Inês Balacó, Tah Pu Ling, Cristina Alves
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Thoracolumbar kyphosis(TLK) has a high prevalence amongst children with achondroplasia. We aimed to to analyze the natural history of TLK in patients with achondroplasia followed in our institution.

We reviewed records of patients from 2008 to 2022. Inclusion criteria were presence of clinical TLK and existence of spine radiographs.

Exclusion criteria: lack of 2 consecutive spine radiographs(29 patients), absence of TLK(3 patients), walking age registry(8 patients).

We assessed age, apical vertebra, angle between T12-L1 and T11-L1, apical vertebra wedging(AVW) and walking age.

Fourteen patients were included. Median age on the first radiograph was 17.5(10.0-24.0) months and 20.5(17.0-31.0)months on walking age.

At the time of the first radiograph, median T12-L1 angle was 21.7(10.4-33.3)◦, T11-L1 angle was 29.6(15.2-46.4)◦ and AVW was 22.5(3.0-52.3)%.

Within the 24 months after walking age, median T12-L1 angle was 17.6(7.5-42.6)◦, T11-L1 angle was 24.0 (11.5-50.9)◦ and AVW was 35.4(13.0-51.9)%, corresponding to a correction of 24.7(-95.2–58.6)% for T12-L1 and 20.3(-107.8–42.2)% for T11-L1 angles, and a progression of 37.0(-43.5–500.0)% of the AVW. Only 4 (28.6%) and 5(35.7%) patients had progression of the kyphosis at T12-L1 and T11-L1 levels but 10(71.4%) patients had a progression of AVW.

We found a moderate negative correlation between walking age and T12-L1(r=-0.542, p=0,045) and T11-L2(r=-0.593, p=0,025) angles correction.

Four (28.6%) patients started vosoritide within the 24 months after walking age, who tended to have better T11-L1 angle correction but more AVW progression.

Most patients included in the study have correction of the TLK after walking age as previously reported, despite >75% having a progression of the AVW.

II.4 Clinical and molecular characterization of 17 patients with acrodisostosis and genotype-phenotype correlation *(8'+2')*

André Abreu (1), Federica Tamburrino (2), Lisette Leeuwen (3), Livia Garavelli (4), Gabriele Trimarchi (4), Maria Elisabeth Street (5), Stefano Giuseppe Caraffi (4), Lucrezia Giannini (4,6), Maria Chiara Baroni (4), Sergio Bernasconi (7), Marzia Pollazzon (4), Roberta Zuntini (4), Maria Abreu (8), Renata Oliveira (9), Erica H. Gerkes (10), Oana Moldovan (11), Patrícia Dias (11), Marta P. Soares (11), Catarina Macedo (11), Brígida Robalo (12), Carla Pereira (12), Karen E. Heath (13-15), Ana Berta Sousa (1,11), André M. Travessa (1,11)

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Acrodisostosis is a rare skeletal dysplasia characterized by short stature, severe brachydactyly, facial dysostosis, and variable hormone resistance, caused by monoallelic pathogenic variants in the *PRKAR1A* and *PDE4D* genes. Here, we aim to clinically and molecularly characterise a cohort of patients with acrodysostosis, compare these findings with existing literature, and confirm or identify novel genotype-phenotype correlations by analysing them.

Methods:

We conducted a retrospective observational study of 17 patients with genetically confirmed acrodysostosis, compiling comprehensive clinical, radiological, and molecular data. Additionally, we performed a systematic review and statistical analysis of published cases, comparing clinical manifestations according to the affected gene, gene domain, and variant type.

Results:

We included 10 patients with *PRKAR1A* variants and 7 with *PDE4D* variants, revealing both shared and gene-specific features. Our cohort and literature review showed a higher frequency of short stature, behavior problems, and endocrine abnormalities in patients with *PRKAR1A* variants. *PDE4D* variants, especially those in the UCR1 domain, were linked to a higher prevalence of intellectual disability. In addition, we found evidence for gene-specific differences in facial phenotype. A significant number of patients with thrombophilia are reported in the literature, and two cases of osteoporosis/osteopenia were observed in our cohort, suggesting that these features should be considered in the clinical surveillance of these patients.

Conclusions:

This study expands the clinical and molecular spectrum of acrodysostosis and provides new evidence for gene- and domain-specific genotype-phenotype correlations. Our findings highlight the importance of detailed phenotypic reporting for prognostic counselling and surveillance strategies for affected individuals.

Keywords: acrodysostosis, genotype-phenotype correlation, *PDE4D*, *PRKAR1A*, skeletal dysplasia.

II.5 *Familial short stature and brachydactyly - PRKAR1A Variant of Uncertain Significance (5'+1')*

Raquel Calheiros[1]* & Inês Meira[2], Joana Neto[2], Joana Cardoso[2], Renata Oliveira[2], Rita Santos Silva[2], Cíntia Castro-Correia[2], Pedro Louro[2]

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Background:

Acrodysostosis type 1 (ACRDYS1; MIM#101800) is a rare skeletal dysplasia caused by variants in gene PRKAR*1A* and characterized by short stature, brachydactyly, advanced bone age, and variable resistance to hormones such as PTH, TSH, and GHRH. The clinical significance of some of these variants remains unclear.

Clinical Case:

A 10-year boy was referred to pediatric endocrinology due to concerns about short stature (height 127.5 cm, -1.83 SDS). He was born at term (2690 g, -1.53 SDS; 46 cm, -1.85 SDS), with unremarkable perinatal history. His neurodevelopment is normal and he has an excellent academic performance. On physical examination, he had small hands and feet with shortening of the 4th and 5th metacarpals and metatarsals on the right side. No facial dysmorphisms or spinal deformities were noted. Laboratory's evaluation showed normal calcium/phosphate levels, but persistently elevated PTH (114.6 pg/mL) with normal vitamin D, suggesting possible PTH resistance. Other hormonal axes (thyroid, adrenal, GH) were normal; his bone age was advanced (12 years and 6 months, +2 SD). The genetic testing identified a novel heterozygous variant of uncertain significance in *PRKAR1A* [NM_002734.5(*PRKAR1A*):c.466G>T p.(Val156Phe)], also found in the mother (who has short stature (138.9 cm, -3.74 SDS) and hands and feet brachydactyly with shortening of the 4th and 5th metacarpals and metatarsals.

Conclusion:

This family phenotype resembles acrodysostosis type 1 diagnosis, and the *PRKAR1A* variant identified let us toward its validation. However further discussion and family follow-up and segregation analysis would be necessary to clarify the pathogenicity of this variant as this genetic testing might confirm the diagnosis of ACRDYS1.

II.6 Epiphyseal Dysplasia with Sideroblastic Anemia: a mild presentation of EVEN-plus, or an entirely new entity? *(5'+1')*

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Introduction

Deleterious *HSPA9* variants have been associated with autosomal dominant/recessive sideroblastic anemia (SdA), and autosomal recessive EVEN-plus syndrome. EVEN-plus syndrome is characterized by the association of spondyloepiphyseal dysplasia, facial dysmorphism and other, variable, malformations. These two entities have been described independently, but not together, although loss of gene function appears to be the pathogenic mechanism associated with both disorders.

Clinical case

We report the clinical case of two male siblings, diagnosed with spondyloepiphyseal dysplasia (SED) and early-onset SdA, of varying severity, who were initially investigated separately. Although the children did not exhibit a facial gestalt suggestive of the disorder, WES was performed due to the co-occurrence of SED and SdA. This led to the identification of two *HSPA9* variants of unknown significance (VUS), in trans, confirmed through parental studies: NM_004134.7:c.[228G>A];[1073T>C], p.[(Lys76=)];[(Leu358Pro)]. Splicing assays in blood revealed that the synonymous variant induced an anomalous splice site, with consequent loss of function, r.215_228del p.(Lys73Alafs*21), which allowed for variant reclassification as pathogenic. This also permitted reclassification of the second variant to likely pathogenic and a molecularly confirmed diagnosis.

Discussion

As such, we present two siblings with an apparently mild EVEN-plus phenotype, no suggestive facial gestalt, and SdA. SdA is not a recurring finding in reported individuals with EVEN-plus syndrome, even though it could be expected considering both entities have the same pathogenic mechanism. This may be due to the difficulty of diagnosing mild cases of SdA, or it may be that the complete loss of function of the gene induces a different haematological phenotype.

II.7 Hajdu-Cheney syndrome: a familial case with possible new findings

(5'+1')

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Theme: Case of Hajdu-Cheney Syndrome

Abstract: Hajdu-Cheney syndrome (HCS) is a skeletal dysplasia clinically characterized by acro-osteolysis, osteoporosis, short stature, craniofacial abnormalities, dental anomalies, neurodevelopmental disorders, renal cysts, and other features. HCS is caused by heterozygous pathogenic variants in the *NOTCH2* gene.

We report the case of a 45-year-old man referred for evaluation due to recurrent fractures. Family history is notable for a son exhibiting a similar phenotype and associated learning difficulties.

On personal history, he had congenital coxa valga, chronic venous disease, hyperCKemia, high myopia, strabismus, and astigmatism. He currently has severe osteoporosis, degenerative osteoarticular disease, chronic pain, and limited mobility.

On observation, his height is 153 cm, and he has hypodontia, fragile and yellow teeth, short trunk, hyperkyphosis and hyperlordosis, jont laxity, brachydactyly, and sebaceous cysts.

A skeletal dysplasia panel was performed and identified the pathogenic variant c.6622C>T p.(Gln2208*) in heterozygosity in the *NOTCH2* gene, establishing the diagnosis of HCS. This variant was confirmed to be present in his affected son.

This familiar case highlights the clinical variability of HCS. The diagnosis allowed us to guide multidisciplinary surveillance and treatment for the patient, as well as genetic counseling and follow-up for his son. High myopia and hyperCKemia have not previously been described in association with HCS, yet were observed in both, the patient and his affected son; additional cases are needed to determine whether these features are part of the HCS phenotypic spectrum.

II.8 *COL27A1* Variants in a Child with Severe Scoliosis *(5'+1')*

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Steel syndrome (MIM# 615155) is a rare autosomal recessive skeletal disorder associated with biallelic pathogenic variants in COL27A1. This gene encodes collagen type XXVII alpha-1 chain, a structural component in cartilage and bone development. Clinical features include hip and radial head dislocations, carpal coalition, scoliosis, short stature, and facial dysmorphism.

We report a 9-year-old girl with congenital torticollis, bilateral hip dysplasia and progressive severe scoliosis, which required surgical correction at age of 6. Initial suspicion of juvenile idiopathic arthritis was excluded after rheumatologic evaluation. She was also recently diagnosed with centrotemporal spike epilepsy.

Genetic testing initially identified a variant of uncertain significance (VUS) in the *COL2A1* inherited from an unaffected parent, and therefore unlikely to explain the phenotype. Further next-generation sequencing (NGS) targeting genes associated with skeletal dysplasia identified two heterozygous VUS in *COL27A1*: a missense variant NM_032888.4:c.2207G>T p.(Gly736Val) in exon 9 and a duplication spanning exons 14 to 35. Compound heterozygosity was confirmed.

This case report illustrates a possible clinical variability of *COL27A1*-related skeletal dysplasia and highlights the importance of comprehensive genetic evaluation in children with complex skeletal anomalies, such as severe scoliosis. It also expands the known *COL27A1* mutational spectrum. Although the identified variants might partially explain the patient´s phenotype, we cannot confirm the clinical diagnosis, as the variants are currently classified as VUS. Given the role of *COL27A1* in bone and joint development, early recognition and intervention are essential to optimize care. Continued clinical and genetic investigations is crucial to improving diagnosis, prognosis, and management strategies.

II.9 Bone Cysts in Juvenile Paget's Disease: Atypical Manifestation or Incidental Finding? *(5'+1')*

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Juvenile Paget's disease (JPD) is a rare metabolic bone disorder (< 1:10 million) characterized by markedly increased bone turnover. Clinical manifestations typically include bone deformities, cortical expansion, pain and pathological fractures. Bisphosphonates have shown efficacy controlling disease activity and symptoms.

We report a female patient diagnosed with JPD at 33 months old (genetically confirmed), presenting with frequent falls, leg deformities and lower limb pain. She achieved good clinical and biochemical response to bisphosphonate therapy. At age 23, she developed severe bilateral leg pain, hard swelling over the anterior tibial surfaces, with no inflammatory signs, and only a slight increase in alkaline phosphatase (AP). Although bone scintigraphy suggested early Paget lesion, Computerized Tomography scan and Magnetic Resonance Imaging revealed simple bone cysts (SBC) within the tibial diaphysis. She consistently experienced pain relief after each annual zoledronate infusion, alongside stable AP levels.

To our knowledge, SBC have not been previously described in the context of JPD. However, a potential link may exist, as one proposed pathophysiological mechanism involves impaired venous drainage in areas of high bone turnover. While malignant transformation is rare, their presence may increase the risk of pathological fractures (>30% - location dependent).

JPD follows a chronic course, warranting lifelong surveillance. This case highlights the importance of regular follow-up not only for monitoring disease activity, but also identifying complications that may impact prognosis and management. Further reports and registry data are needed to determine whether this represents a rare complication or an underrecognized feature of JPD.

15:40—16:10 Comunicações orais - Casuísticas e Casos Clínicos III / *Oral communications - Clinical Cases III* (PT/EN)
Moderação / *Moderation*: Lina Ramos, ULS Coimbra, Luis Abreu, ULS Coimbra

III.1 Curved Insights: Prenatal Detection of Campomelic Dysplasia and the Complexities of Early Diagnosis (8'+2')

Ana Filipa David, ULS Coimbra

III.2 Unraveling the Fragility: Rare Clinical Cases of Osteogenesis Imperfecta Types III/IV and the Challenges of Prenatal Diagnosis (8'+2')

Carlota Anjinho Carvalhos, ULS Coimbra

III.3 Spotting the Punctate: Rare Clinical Cases of Chondrodysplasia Punctata and Diagnostic Dilemmas (5'+1')

Inês Mariano, ULS Coimbra

III.1 Curved Insights: Prenatal Detection of Campomelic Dysplasia and the Complexities of Early Diagnosis *(8'+2')*

Ana David[1], Inês Marques Mariano[2], Ana Rita Matos[3], Filipa Nunes[2,4], Joaquim Sá[5], Filipa Marques[2,4], Miguel Branco[2,4], Fabiana Ramos[4,5]

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Introduction

Campomelic dysplasia (CD) is a rare and often lethal skeletal dysplasia caused by heterozygous pathogenic variants in the *SOX9* gene. It is characterized by bowed long bones, craniofacial abnormalities, and, in some cases, disorders of sex development in fetus 46, XY. Prenatal diagnosis remains challenging due to phenotypic variability and overlap with other skeletal disorders.

Methods

We conducted a retrospective review of four fetuses with prenatal suspicion and molecular confirmation of CD, referred to a tertiary center. Data were collected from medical records, including ultrasound findings between 12 and 22 weeks of gestation, genetic testing, and fetal autopsy, when performed.

Results

All cases involved healthy, non-consanguineous couples with spontaneous pregnancies. Suspicion arose between 12 and 21 weeks. Ultrasound findings included bowed femurs (3/4), micrognathia (2/4), cleft palate (1/4), cystic hygroma or increased nuchal translucency (4/4), talipes (2/4), and kyphoscoliosis (1/4). Hydrops fetalis was present in two cases. Molecular confirmation was achieved in all cases, identifying four distinct *de novo* pathogenic variants in *SOX9*. Termination of pregnancy was performed in all cases (13–22 weeks). Fetal radiography (3/4) revealed curved long bones, tibial spurs, and scapular anomalies. Autopsy (3/4) confirmed classic CD features with no major visceral anomalies. One case was suggestive of acampomelic campomelic dysplasia.

Conclusions

CD should be considered in fetuses with 'bent bone' dysplasia, particularly when associated with facial dysmorphism or lymphatic anomalies. Early multidisciplinary evaluation and timely molecular testing are essential for accurate diagnosis and genetic counseling.

Keywords

Campomelic dysplasia; Prenatal diagnosis; *SOX9* gene; Skeletal dysplasia; Bent bones.

III.2 Unraveling the Fragility: Rare Clinical Cases of Osteogenesis Imperfecta Types III/IV and the Challenges of Prenatal Diagnosis *(8'+2')*

Ana Rita Matos[1], Carlota Anjinho Carvalhos[2], Ana David[3], Inês Marques Mariano[2], Ana Cláudia Santos[2,4], Miguel Branco[2,4], Lina Ramos[4,5], Fabiana Ramos[4,5]

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Introduction

Osteogenesis imperfecta (OI) is a rare genetic connective tissue disorder characterized by bone fragility and recurrent fractures, with a prevalence estimated at 1 in 10,000 to 1 in 20,000 births. Clinically, OI presents a spectrum from mild to severe forms. Around 90% of cases result from dominant mutations in the *COL1A1* and *COL1A2* genes affecting type I collagen synthesis. Prenatal diagnosis of non-lethal OI (OI type II) remains challenging due to phenotypic variability and overlapping features with other skeletal dysplasias, which can complicate counseling and management decisions.

Methods

We reviewed three cases, referred to our hospital, with prenatal suspicion of skeletal dysplasia and molecular confirmation of OI type III/IV. Data were obtained from clinical records, including ultrasound findings, genetic analysis, and fetal autopsy.

Results

All cases involved non-consanguineous couples, nulliparous women and *de novo* pathogenic variants. Ultrasound scan between 20 and 22 weeks revealed bilateral femoral bowing and shortening in all fetuses, with additional limb involvement in two cases. Molecular confirmation was achieved through trio exome sequencing, identifying two distinct *COL1A2* and one *COL1A1* variants. Case 1 showed isolated femoral involvement with no fractures but reduced mineralization. Case 2 exhibited more severe features, including multiple fractures, cleft palate and blue sclerae. Case 3 had bowed femurs and short long bones without fractures. All pregnancies were terminated between 22 and 24 weeks.

Conclusion

These cases illustrate the phenotypic variability of OI type III/IV and the importance of combining imaging and genetic testing for accurate diagnosis. Early genetic confirmation supports counseling and planning, with low recurrence risk due to *de novo* variants in all cases.

III.3 Spotting the Punctate: Rare Clinical Cases of Chondrodysplasia Punctata and Diagnostic Dilemmas *(5'+1')*

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Introduction:

Chondrodysplasia punctata (CDP) comprises a group of clinically and genetically heterogeneous skeletal dysplasias characterized by epiphyseal stippling, limb shortening, and craniofacial anomalies. The X-linked dominant subtype (CDPX2), the Conradi-Hunermann Syndrome, primarily affects females with asymmetric limb shortening, ichthyosis, scoliosis, and facial dysmorphism, while the X-linked recessive form (CDPX1) affects males, presenting with distal phalangeal and nasomaxillary hypoplasia alongside stippled epiphyses. We report two prenatal cases of genetically confirmed CDP, highlighting the role of integrated sonographic evaluation and molecular testing in diagnosis and management.

Methods:

Ultrasound examinations were performed between 21 and 22 weeks of gestation with standard fetal biometric measurements and fetal sex determination. Amniocentesis was performed for chromosomal microarray and skeletal dysplasia gene panel analysis. Postmortem examinations followed medical termination of pregnancy.

Results:

In the first case (22 weeks + 1 day), ultrasound revealed midface hypoplasia, thoracic vertebral straightening with spinal canal narrowing and marked shortening of long bones below the 1st percentile. Early trochanteric ossification was also noted. Chromosomal microarray detected a 5.89 Mb deletion at Xp22.33 involving *STS*, *ARSE*, and *NLGN4X* genes, consistent with CDPX1. The second case (21 weeks + 6 days) showed shortened femur and humerus with abnormal proximal epiphyseal ossification. Molecular analysis identified a heterozygous likely pathogenic variant in the *EBP* gene (c.388G>A; p.Gly130Arg), confirming CDPX2. Both pregnancies were electively terminated after counseling.

Conclusion:

These cases demonstrate the genetic and phenotypic diversity of CDP. Integrated prenatal imaging and molecular diagnostics enable accurate subtype classification, aiding prognosis, counseling, and management.

Keywords: Chondrodysplasia punctata; skeletal dysplasia; prenatal diagnosis; genetic testing; X-linked inheritance; amniocentesis