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3ªs Jornadas de Doenças Ósseas Raras

Livro de Resumos

C1. Tibial dysplasia – Etiology does matter.

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Introduction and Objectives

Tibial dysplasia with anterolateral bowing is a rare deformity (1:190.000) that may lead to pseudarthrosis and fracture. It is often misgeneralized as congenital pseudarthrosis of tibia (CPT), but commonly doesn't present with an unhealed tibia at birth. Anterolateral tibial bowing may be idiopathic or related with Neurofibromatosis Type I, fibrous dysplasia, amnionic band syndrome, or combined with polydactyly (CATBP). CATBP represents a distinct entity with a benign prognosis that should not be confused with other conditions to avoid unnecessary investigations or overtreatment.

The authors describe the case of a boy with CATBP.

Case report

The patient was referred to our Outpatient Clinic at 18-month of age for right tibial bowing, leg length discrepancy and pre-axial foot polydactyly. Physical exam showed 2 café-au-lait spots and 1 nevi, no axillary freckling. The boy walked with a slight limp. Radiographs showed anterolateral tibial bowing with medullary sclerosis with preserved cortical diameter and structurally normal and straight fibula (Crawford&Schorry type I). There was also a duplication of the great toe distal phalanx. NF1 gene study showed no mutation. The child underwent surgery at 3.5 years for correction of hallux varus and extra-toe excision. Currently, at age of 11, he has an estimated 3.5cm leg length discrepancy (uses 1,5cm shoe lift), prominent fibular head, stopped bracing (which was maintained after age of 2). He started playing sports and the deformity of his tibia has been improving.

Discussion and Conclusion

CATBP is a rare but recognizable entity that presents with anterolateral tibial bowing. It is generally associated with a favorable prognosis. The etiology for CATBP remains uncertain: all published cases have been isolated, with no recurrence in sibships, no associated cytogenetic abnormalities or parent to child transmission, which suggests a developmental abnormality. The diagnosis is made clinically based on physical and radiographic findings and is important to prevent unnecessary procedures (normally required in NF-1).

C2. Pregnancy and breastfeeding in 3M syndrome

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Three M syndrome is a rare autosomal recessive disorder characterized by severe pre- and postnatal growth deficiency, skeletal abnormalities, characteristic facies, and normal intelligence. Males may have gonadal dysfunction with oligo/azoospermia and hypospadias. Females, however, have normal gonadal function. Only two reports of pregnancy management in 3-M syndrome have been published.

A 41-year-old nulliparous woman with short stature [1,18m (<3rd percentile)] and macrocephaly [49cm (>99th percentile)] was seen for prenatal and genetic counselling due to her 3-M syndrome confirmed by the genetic testing: homozygous likely pathogenic c.35dup (p.Cys13Valfs*241) at *OBSL1*. She underwent four orthopaedic surgeries. Her parents were consanguineous (first cousins) with normal stature. Her healthy nonconsanguineous husband opted not to perform carrier analysis for 3-M.

She presented to the Obstetric Department at 42-years-old, at 18 weeks gestation. Ultrasounds, standard prenatal blood and non-invasive prenatal screening tests were normal. She was seen on follow-up at standard intervals and had a pre-anaesthetic consult. At 37 weeks gestational hypertension was diagnosed. At 37+2 weeks a caesarean section was performed under continuous spinal anaesthesia by intrathecal catheter, without intercurrences.

She delivered a healthy male infant (weigh 2470g; length 45,5cm; head circumference 33,5cm). Apgar score was 7/9/10 at 1/5/10 minutes, respectively. Both were discharged without intercurrences. She did not breastfeed due to concerns of inability and fear of aggravating chronic back pain.

In summary, females with 3-M syndrome have normal gonadal function and can conceive and successfully carry a pregnancy to term. Management of parturients with skeletal dysplasia is challenging, requiring a multidisciplinary team. This case highlights that a timely prenatal breastfeeding consultation should be included in pregnancy management.

C3. *TBCE*-associated bone dysplasia? The importance of clinical suspicion in skeletal dysplasias.

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Report of a 27yo woman, born at term, with weight, length and head circumference just below 5th centile. Independent walking age was 18 months with developmental milestones otherwise normal. At four years of age, she initiated recurring generalized muscular pain and mild muscular weakness warranting follow-up in Neurology. She later developed severe scoliosis, surgically interventioned, restrictive ventilatory syndrome, and recurring diverticulitis. Serum calcium was persistently below reference levels. Muscle biopsy was abnormal but nonspecific. Congenital myopathy gene panel disclosed a heterozygous VUS in *RYR1*, inherited from a healthy parent. Upon physical examination in Medical Genetics during adulthood she presented proportionate short stature (135cm), low weight (33.5kg), and small OFC (52cm). All limb segments were <5th centile. Hands and feet were very small. Skeletal survey showed long thin clavicles, narrow thoracic grid and thin ribs, hypoplastic trochleae and valgism of the hip, as well as mild medullary stenosis of the fibula. This clinical picture prompted skeletal dysplasia investigation. WES-based gene panel identified two variants in compound heterozygosity in *TBCE* (NM_003193.5:)*:* c.636_639del, frameshift, likely pathogenic and c.372-10T>C, splicesite, VUS. The latter was novel and in silico predictors supported a deleterious effect.

This patient's skeletal features were previously presumed to be secondary to an undiagnosed neurological condition, however, phenotype and genotype reappreciation points towards *TBCE*-related Kenny-Caffey syndrome (MIM#244460) that also manifests with hypocalcemia. In this case, the input of skeletal dysplasia experts is of the utmost importance towards establishing the diagnosis.

C4. Pfeiffer Syndrome: a family report illustrating a highly variable expressivity related to *FGFR1* p.Pro252Arg variant

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ABSTRACT:

Introduction: Pfeiffer syndrome (PS) is an autosomal dominant skeletal disorder, classically characterized by craniosynostosis, facial dysmorphisms, and digital anomalies. PS is caused by pathogenic variants of *FGFR* genes. In last years, a wide range of manifestations, with or without craniosynostosis, has been reported. Additionally, extra-skeletal manifestations including eye, auricular, respiratory, cardiovascular, gastrointestinal, and genitourinary anomalies have been observed.

Case report: A late premature male neonate was transferred from Azores to a tertiary NICU due to feeding intolerance secondary to partial duodenal membrane, requiring surgical correction. He also had deviated great toes, and syndactyly of 2/3 toes on the left, and 2/3/4 on the right, which prompted genetic referral. He had no other dysmorphic features. Evaluation of family history revealed syndactyly and deviated broad thumbs and toes in four generations (father, cousin, grandfather, and great-grandfather), and second cousin diagnosed with PS, associated to a common *FGFR1* pathogenic variant (p.(Pro252Arg)). We hypothesized that the proband congenital anomalies and the familial digital anomalies were manifestations of the PS spectrum, being all related to the familial *FGFR1* variant. Molecular analysis of proband and his father confirmed the presence of p.Pro252Arg variant. Craniosynostosis was excluded, and genetic counselling was provided to parents.

Conclusion: Variable expressivity can complicate the recognition of PS. Careful phenotyping and acknowledgment of family history are necessary. Genetic counselling is also required to inform the PS families about the 50% risk of transmission, the possibilities of the anomalies that may occur in future pregnancies, and the extreme clinical variability.

C5. Osteochondromas: Multiple Problems

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Introduction:

Multiple osteochondromas (MO) is a rare autosomal dominant disorder (ORPHA:321) . Causative variants in *EXT1* or *EXT2* genes are identified in 85-90% of cases. There are family history of MO in most cases but in 10% the variants are *de novo*/sporadic. Osteochondromas develop from the metaphyses of long bones and increase in size in the first decade of life, and usually cease to grow when the growth plates close at puberty. They are pedunculated or sessile (broad base) and can vary widely in size. The risk of malignant degeneration to osteochondrosarcoma is low, although it increases with age. We present a case of a boy with MO, without family history, and describe some challenges in his orthopaedical management.

Clinical case:

An eleven-year-old male with multiple osteochondromas, diagnosed since the age of three, was referred to our Outpatient Clinic. Both parents and brothers were not affected. Genetic testing found a *de novo* pathogenic heterozygous variant in the *EXT1* gene (c.962+1G>C). He underwent surgery on the right forearm, performed in another institution at age nine. When we first observe him, he complained of limited pronosupination of the right forearm and right knee pain. Upper limb radiographs showed a curved bilateral radius, with radial head subluxation and ulnar minus wrist, worse on the right side. Lower limb radiographs revealed a right *genu varum* and sessile osteochondromas in the distal femur and proximal tibia.

A distal radius osteotomy and right knee lateral distal femur hemiepiphysiodesis were simultaneously performed. The femur implant was removed one-year post-surgery, after normal and symmetric lower limb alignment had been achieved.

Patient is now 13 years of age with no functional complaints and maintain normal lower limb alignment. Although he has radial head dislocations, he does not feel pain or functional impairment in his daily life activities. During his most recent clinic appointment, he complained of 2 transitory episodes of lower limb paresthesia. For this reason, a spine MRI has been scheduled, in order to identify any possible spinal cord compression due to possible intracanalar lesions.

Conclusion:

We present a rare case of a sporadic multiple osteochondromas. Despite their benign nature in MO, osteochondromas may cause reduction in skeletal growth, bone deformities, shortened stature, premature osteoarthrosis and compression of peripheral nerves. Therefore, pediatric patients must be closely followed. During follow-up, radiographs should only be obtained when symptoms or changes in limb alignment or range of motion are apparent, in order to protect these patients from excessive ionizing radiation. Surgery to resect the osteochondromas should be carried out to treat pain or prevent joint instability or restricted range of motion.

C6. *COL1A2* multiexon deletion in Osteogenesis Imperfecta type 2 – clinical case

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CONTEXT: Osteogenesis Imperfecta (OI) is characterized by liability to bone fractures mainly due to pathogenic variants in genes that encode collagen type I alpha1 and alpha2 chains – *COL1A1* and *COL1A2*. OI type 2 is at the most severe end of the clinical spectrum of OI usually leading to death during the perinatal period and is typically caused by a dominant-negative effect of glycine substitutions in the triple helical domain.

CASE REPORT: We report the first pregnancy of a healthy and non-consanguineous couple with a high combined first-trimester trisomy 21 risk and ultrasound anomalies detected at 13 weeks - nuchal translucency above the 99th percentile, subcutaneous edema of lower limbs with shortening of the long bones and bilateral clubfeet. Later, detection of bowing of the long bones, low amniotic fluid with reduction of fetal movements and an abdominal circumference below the 5th percentile led the couple to opt for termination of pregnancy. Post-mortem radiological studies confirmed the diagnosis of OI type 2. Molecular studies identified a heterozygous multiexonic *COL1A2* deletion (exons 4 to 17). This deletion was also detected in the healthy mother, in mosaic state, who also carries a second mosaic multiexonic deletion (exons 12 to 17) in the same gene. RNA studies from the mother's fibroblasts confirmed the presence of both deletions and demonstrated that they were both in-frame.

CONCLUSION: This case expands the current molecular knowledge of collagen type I mutations reinforcing the role of multiexonic deletions in OI type 2. This clinical case also illustrates the challenges in prenatal diagnosis of fetuses with OI type 2 and highlights the importance of molecular studies, including familiar studies, to provide accurate genetic counselling to these families.

C7. Autosomal-Recessive Mutations in *MESD* – A Clinical Case of Severe Osteogenesis Imperfecta

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Introduction:

Early-onset scoliosis (EOS) is defined as a spinal deformity occurring before 10 years old. Untreated EOS or early spinal fusion in a short spine are associated with pulmonary compromise. The spine, thoracic cage and lungs growth are closely associated with each other and the length of the thoracic spine is critical for the lung development. So the EOS treatment goals are to increase respiratory capacity and control deformity.

Surgical management of spinal disorders in sclerosing skeletal dysplasias is a challenge because of extremely hard bone and higher risk of postsurgical complications.

Case Presentation:

We presented a case of a girl that presented at birth: cleft palate, heart defect, ulnar deviation of the third finger of left hand, micrognathia and macrocephaly. Until 6 years old she also developed severe and progressive scoliosis, transmission hearing loss, obstructive apnoea and headaches. The initial proposed diagnosis was Catel-Manzke syndrome, not confirmed by clinical and radiological evolution. Despite continuing without an established diagnosis, due to a progressive and severe EOS with restricted pulmonary syndrome, at four years old she was submitted Osteopathia Striata with Cranial Sclerosis was raised. The suspicion came from the radiodense longitudinal striation at the metaphysis of the tubular bones and its equivalent of the axial bones concurrent with craniofacial hyperostosis. Molecular studies and Genetic Counselling was made and the diagnosis was established by identifying recurrent nonsense mutation (*de novo* WTX mutation p.R358*) with patients documented with a phenotype similar to ours. The genetic counselling was made to her and her parents. At 13 years old, she was graduated with an instrumented final fusion. Spontaneous arthrodesis was found, requiring several vertebral osteotomies and a lengthy and difficult procedure. Nevertheless, an additional sagittal deformity correction of 25% was obtained and thoracic spine height increased 16mm. Sixteen months after definite surgery, she is without complaints, without complications.

Discussion:

Discussion and a multidisciplinary approach were decisive in the treatment of this Patient. A diagnosis of bone-forming bone dysplasia could be obtained and prepared the Paediatric Orthopaedic Surgeons for the osteotomies required at the final procedure. The initial treatment changed the natural history of the disease (EOS), keeping the thoracic spine height, avoiding worsening of the spinal deformity, and allowing lung development and function. Despite growth friendly and a non- fusion procedure was initially performed, spontaneous arthrodesis limited additional correction and lengthening in final surgery. It would be important to discuss weather patients with this condition could suitable candidates for magnetically-controlled growing rods.

C8. Caffey disease: clinical case with striking neonatal presentation

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Introduction: Caffey disease or Infantile Cortical Hyperostosis (ICH) is a genetic disease characterized by excessive subperiosteal new bone formation typically associated with painful swelling of joints and adjacent soft tissues, fever and irritability. Findings usually appear between birth and five months and tend to resolve spontaneously by the age of two. ICH is caused by a recurrent heterozygous *COL1A1* variant. It is inherited in an autosomal dominant pattern with incomplete penetrance.

Clinical case: We report a case of a female newborn (39+4 WG), without relevant obstetric history (including prenatal ultrasounds). At birth time, she presented with angulated long bones accompanied by deformities, mainly in the legs and forearms, with limited mobility due to pain. X-rays revealed striking subperiosteal cortical hyperostosis of the diaphyses of the long bones (bilateral at tibia/fibula and radial/ulna, unilateral at femur and humerus), apparently with some involvement of the jaw and facial bones and no signs of old or recent fractures. No changes were detected on blood analysis. Targeted genetic testing identified the heterozygous pathogenic *COL1A1* variant, p.(Arg1014Cys), confirming ICH diagnosis. This variant was inherited from an unaffected progenitor. Follow-up at 15 months showed the expected good clinical evolution.

Discussion:
It is unusual to observe such a generalized presentation at birth of ICH. During the neonatal period, it is important to distinguish this condition from other different diagnoses with poorer prognoses and requiring intervention, such as Osteogenesis Imperfecta and (lethal) Caffey dysplasia. Immediate interaction with a skeletal dysplasia reference team allowed us to reach the correct diagnosis, thus reassuring neonatal colleagues and the family.

C9. Fibrous Dysplasia: case series and influence on quality-of-life

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Introduction

Fibrous Dysplasia (FD) is a rare bone disease resulting from mosaicism for a postzygotic mutation in the *GNAS* gene. It can be monostotic or polyostotic, associated or not with extraskeletal findings (McCune-Albright syndrome) or with intramuscular myxomas (Mazabraud syndrome). It has a varied clinical expression, including pain, pathological fractures and deformities. In this study the authors aimed to describe the clinical manifestations of FD and evaluate its impact in Quality-of-Life (QoF) of these patients.

Material and Methods:

Retrospective study including patients diagnosed with DF, treated in one institution, from 2010 to 2021. The studied variables were: demographic data, referral reasons, age at diagnosis, complementary exams, biopsies, treatments performed, follow-up time and complications. QoF was evaluated by Kidscreen-10 questionnaire.

Results:

Twenty-four patients were included, 14 boys, mean age at diagnosis/symptoms was 9 years (2-17), follow-up of 38 months (3-182). Two patients had the McCune-Albright syndrome. Most patients (87.5%) had unilateral pathology (12 right and 9 left). 70.8% had monostotic disease. Location (according to the percentage of patients with affection): femur (70.8%), tibia (50%), 3 craniofacial and 1 spine. 50% had as 1st symptom a pathological fracture (others: 25% pain, 12.5% swelling, 12.5% incidentaloma). Histopathological diagnosis in 71%. Surgery in 75% of patients (mean 2.11 procedures/patient), 58.3% for pathologic or impending fracture, 12.5% for proximal femur deformity. 3 patients were treated with bisphosphonates with improvement of pain. At 12.5 years (8-19) 79.1% are asymptomatic or have mild pain, no limitations in daily life routines and 4 use orthosis or walking aids. Kidscreen-10 was 46 (37-50) in children and 43.5 (25-50) in parents at 14 years (8-23).

Conclusion

Fibrous Dysplasia has a broad and diverse clinical spectrum, posing diagnostic and therapeutic challenges. These patients have a lower QoF than healthy peers and benefit from coordinated multidisciplinary approach in centers with experience and differentiation.

Clinical Relevance:

There is a need to provide personalized medical and surgical treatments for patients with Fibrous Dysplasia.

C10. Assistive products prescription and fibrous dysplasia: a case report

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Introduction: Fibrous dysplasia (FD) is a rare condition, in which the bone is replaced by fibrous connective tissue that weakens its structure, making it abnormally fragile and prone to fracture. Both appendicular and axial skeleton can be affected, with resulting structural abnormalities that might compromise functional capacity.
Case report: The authors present the case of a 21-year-old female with McCune-Albright Syndrome, diagnosed at 8 months of age. The patient had a history of multiple spontaneous fractures and bone deformity, with several corrective surgeries of the limbs.
Regarding functional status, the patient is currently independent in toileting and eating, but dependent in transfer, grooming, dressing and bathing. She is able to independently ambulate in a power wheelchair (WC) with manual control on the right. Functional Independence Measure (FIM) score is 46 (WC) + 35 - 81.
She had bone deformity in both superior and inferior limbs, with joint range of motion limitation, and a severe dorsolumbar scoliosis that resulted in incorrect wheelchair positioning, compromising ambulation. Therefore, a custom-made 2-part molded foam wheelchair seat cushion was prescribed, to optimize patient stabilization in the wheelchair, and improve patient quality of life.
Discussion: Assistive products (AP) are an important tool to maintain or improve function and independence, thereby promoting independent living and quality of life. Although the positive impact of AP at an individual and social level, there are many challenges to its acquisition. Costume-made AP can be adapted to the structural abnormalities resulting from fibrous dysplasia, reducing pain, improving posture, or preventing worsening.

C11. Achondroplasia case series: experience of a paediatric multidisciplinary clinic

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INTRODUCTION: Achondroplasia is the most common form of short stature skeletal dysplasia (1:20,000-30,000) and is caused by a recurrent gain-of-function mutation in *FGFR3* gene. The management of achondroplasia is complex and multifaceted, requiring the coordinated involvement of multiple specialties across the life course to timely act on preventable medical complications and optimize quality of life, autonomy, and independence. Close monitoring during the first 2 years of life is critical.

METHODS: Retrospective and descriptive study of children and teenagers with achondroplasia followed-up in a Portuguese Pediatric Hospital multidisciplinary skeletal dysplasia clinic from 2015, its year of creation, to 2021.

RESULTS: Thirty-eight patients were included, 57.9% boys, age at last observation was 6.89(0.41–19.15) years. All were from Portugal (37%-south, 37%-center, 26%-north). In 2015, age of the 5 referred patients was 8.5 (3.3-14.8) years; in 2021, the 11 referred patients had an age of 1.31(0.1-15.3) years. In only 2 cases (5%), one of the parents also had achondroplasia. In 68.4% of the cases, skeletal dysplasia was suspected in prenatal period. Diagnosis/confirmation was performed prenatally in 18% and in 34% in the neonatal period. At birth, length z-score was -1.40(-3 – +0.10) and 17.6% (6/34) had macrocephaly. At last observation and considering achondroplasia growth curves, weight was -0,01 (-3 - +3) SD and height 0,0 (-2,5 - >+3). Age at the first observation was 3.28(0.09–15.27) years, at the first cranioencephalic magnetic resonance imaging 0.89(0.08–15.8) years and at the first PSG 1.48(0.2–15.6) years. Foramen magnum decompression was performed in 27.3% (9/33) of cases at 0.86(0.38 – 16.1) years. Obstructive sleep apnea syndrome was present in 55% (18/33); 11 started noninvasive ventilation at 0.9(0.2 – 11.0) years. Eighteen (47.3%) underwent adenotonsillectomy. One teenager developed lumbar canal stenosis symptoms and decompression performed at 16.1 years. Limb lengthening was performed in 4/10 teenagers. Twelve participated in observational studies, of which six started experimental treatments in clinical trials setting. Additionally, at least 16 cases subsequently started vosoritide in 2022. Of note, sudden death occurred in one 5-months infant, while being referred to our clinic and was not included in the present study.

DISCUSSION: Centralized care and follow-up of this population by a reference multidisciplinary team allows the increase of experience and better implementation of management international recommendations. This study constitutes the larger achondroplasia cohort described in Portugal. In the future, the impact on this follow-up of specific modifying therapies, one of which was recently approved, will be explored.

C12. Progressive pseudorheumatoid dysplasia: the possibility of misdiagnosis

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Introduction: Progressive pseudorheumatoid dysplasia (PPD, MIM 208230) is an autosomal recessi dysplasia (SED) caused by variants in *CCN6* (formerly *WISP3*). Onset is usually between ages 3 to stiffness and enlargement/ deformity in the absence of inflammation. Typically, the interphalange progression includes large joint involvement and spine osteoarthritis/osteoporosis. Skeletal changes stature. PPD can be misdiagnosed with juvenile idiopathic arthritis (JIA).

Case description: 31-year-old male referred to Genetics due to SED. Second son of a consanguineous couple. At 5 years he complained of stiffness, pain and limited movement of the cervical spine. Skeletal X-rays showed narrowing of intervertebral disc spaces and dorsolumbar spondylosis. He evolved with proximal to distal joint enlargement, deformity and restricted movement in the hands. At 14 years he had bilateral total hip arthroplasty. He was initially diagnosed with JIA, however inflammatory markers were normal and he showed no response to antirheumatic drugs. A skeletal dysplasia NGS panel uncovered an apparently homozygous, likely pathogenic variant of *CCN6* gene: c.1004G>C, p.(Cys335Ser), compatible with a diagnosis of PPD, which is consistent with the patient's phenotype.

Conclusion: It is essential to consider PPD in patients with a combination of non-inflammatory joint disease and characteristic radiographic features, especially those with normal inflammatory markers and who do not improve with antirheumatic drugs. Treatment is supportive, but early diagnosis is essential to prevent long exposure to non-effective systemic medication and to provide adequate genetic counselling.

C13. Therapeutic Approach of Infantile Scoliosis in Osteopathia Striata with Cranial Sclerosis: revisiting a Clinical Case

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Introduction:

Early-onset scoliosis (EOS) is defined as a spinal deformity occurring before 10 years old. Untreated EOS or early spinal fusion in a short spine are associated with pulmonary compromise. The spine, thoracic cage and lungs growth are closely associated with each other and the length of the thoracic spine is critical for the lung development. So the EOS treatment goals are to increase respiratory capacity and control deformity.

Surgical management of spinal disorders in sclerosing skeletal dysplasias is a challenge because of extremely hard bone and higher risk of postsurgical complications.

Case Presentation:

We presented a case of a girl that presented at birth: cleft palate, heart defect, ulnar deviation of the third finger of left hand, micrognathia and macrocephaly. Until 6 years old she also developed severe and progressive scoliosis, transmission hearing loss, obstructive apnoea and headaches. The initial proposed diagnosis was Catel-Manzke syndrome, not confirmed by clinical and radiological evolution. Despite continuing without an established diagnosis, due to a progressive and severe EOS with restricted pulmonary syndrome, at four years old she was submitted to a surgery, a subcutaneous Traditional Growing Rods application. Between the first surgery until 11 years old she was submitted to five surgical distractions – the last two were increasingly less effective. With these procedures we managed to control the disease, the thoracic spine height/pelvic width percentile crossed from a range close to 5 to a percentile above 50, compatible with pulmonary development. During this process, the case was reviewed and at Portuguese Society of Human Genetics meeting and the hypothesis of Osteopathia Striata with Cranial Sclerosis was raised. The suspicion came from the radiodense longitudinal striation at the metaphysis of the tubular bones and its equivalent of the axial bones concurrent with craniofacial hyperostosis. Molecular studies and Genetic Counselling was made and the diagnosis was established by identifying recurrent nonsense mutation (*de novo* WTX mutation p.R358*) with patients documented with a phenotype similar to ours. The genetic counselling was made to her and her parents. At 13 years old, she was graduated with an instrumented final fusion. Spontaneous arthrodesis was found, requiring several vertebral osteotomies and a lengthy and difficult procedure. Nevertheless, an additional sagittal deformity correction of 25% was obtained and thoracic spine height increased 16mm. Sixteen months after definite surgery, she is without complaints, without complications.

Discussion:

Discussion and a multidisciplinary approach were decisive in the treatment of this Patient. A diagnosis of bone-forming bone dysplasia could be obtained and prepared the Paediatric Orthopaedic Surgeons for the osteotomies required at the final procedure. The initial treatment changed the natural history of the disease (EOS), keeping the thoracic spine height, avoiding worsening of the spinal deformity, and allowing lung development and function. Despite growth friendly and a non- fusion procedure was initially performed, spontaneous arthrodesis limited additional correction and lengthening in final surgery. It would be important to discuss weather patients with this condition could suitable candidates for magnetically-controlled growing rods.

C14. Intrafamilial and intragenotypic variability of skeletal ciliopathies: a case-report of the Elis-van Creveld syndrome.

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Abstract:

Skeletal dysplasias and ciliopathies are two types of hereditary disorders that often overlap in their presentation. Since abnormally functioning primary cilia can compromise cell signaling during skeletal development, a subgroup of these conditions, termed skeletal ciliopathies, was proposed. These conditions have highly variable expressivity, even within family members bearing the same causal variants. Here, we report a familial case of two brothers presenting with distinct manifestations of the same skeletal ciliopathy. The younger brother was referred to the Genetics clinic at 19 months of age due to global developmental delay, small stature, non-specific facial dysmorphisms, bilateral hand post-axial polydactyly and syndactyly, and toe nail hypoplasia. The older brother was observed at 11 years of age in our clinic due to his family history, and presented with attention-deficit and hyperactivity disorder, bilateral hand and foot post-axial polydactyly and syndactyly (surgically corrected), incisive teeth agenesis and malrotation, distinct facial features from his brother, and no short stature. Neither brother had any chest, heart or genitourinary abnormalities. Genetic testing was remarkable for two likely pathogenic/pathogenic variants in the *EVC* gene. Compound heterozygosity was confirmed after testing the mother and father, neither of which had any symptom or relevant prior medical history. This confirmed the diagnosis of Ellis-van Creveld syndrome (EVC), a chondroectodermal dysplasia that occurs due to impaired EVC-mediated sonic hedgehog signaling in the cilia of endochondral and skeletal precursor cells. This case not only illustrates the phenotypical variability, but also the intrafamilial and intragenotypic variability of the ectodermal features of this condition.

C15. Trevor disease – conservative vs surgical treatment

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OBJECTIVE:
Dysplasia epiphysealishemimelica (DEH) – Trevor disease, is a rare developmental disorder of childhood and is characterized by asymmetric overgrowth of the epiphyseal cartilage of the epiphyses. It affects 1 in 1000000 individuals andit's more common in males (M:F = 3:1).

Diagnosis is made through the imagiologic study of the affected joint, and the treatment is defined by the severity of symptoms.

We aim to present two cases of Trevor disease, with different treatment options.

MATERIAL and RESULTS:
Case 1: 6 year-old male, presents with an hard retromaleolar lump, painful with deep palpation, after an ankle sprain. Imaging (Xray, MRI and CT scan) showed an exostosis on the medial talar dome, intraarticular, shaping the distal tibial epiphyses. He underwent arthroscopic resection of the lesion, with complete recovery at 4 weeks post-op. Oxford Ankle Foot Questionnaire: Child 0 Parents 0 (10 months post op).

Case 2: 6 year-old male, presents with hard medial ankle lump, with sporadic pain (asymptomatic for 6 months at the time of the first appointment in our Clinic). Imagiing showed an exostosis on the medial and posterior talar dome, intraarticular. Options were discussed with the family: surgery or observation. As the boy became asymptomatic, observation was elected and maintained. At 3 years follow-up, the patient is still asymptomatic. Oxford Ankle Foot Questionnaire: Child 0 Parents 10%.

CONCLUSION:
The differential diagnosis of talar exophytic lesions should entail Trevor disease. The management of these patients should be discussed with the Family, and surgical treatment proposed only in symptomatic patients.

RELEVANCE: Trevor disease is a rare disease with controversial treatment options. We present two similar cases with good outcomes with different management.

C16. Recessive Multiple Epiphyseal Dysplasia – Clubfoot as a Trigger

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Objective:
Recessive Multiple Epiphyseal Dysplasia (EDM4/rMED) is a diagnosis based on clinical, radiographic and molecular findings, usually established during childhood or early adulthood. Approximately 50% of affected individuals have an abnormal finding at birth: clubfoot, clinodactyly, or (rarely) cystic ear swelling. However, only half of those with findings at birth are suspected of having a skeletal dysplasia. Onset of articular pain is variable but usually occurs in late childhood. Our aim is to present a case of rMED in a baby boy referred to our outpatient clinic for clubfoot treatment.

Case report
We report a case of an 18-month-oldboy, diagnosed with bilateral clubfoot at birth, Pirani 6. He was treated with *Ponseti* method, modified for atypical clubfeet, with 9 casts per foot and percutaneous Achilles tenotomy. After the casting phase, he used boots-and-bar. After one year follow-up, a left foot relapse was observed. His stiff feet, associated with valgus knees, short stature and suggested a genetic condition like a skeletal dysplasia. In the Genetics Consultation, his parents confirmed that the boy had had cystic ear swelling in the first months of life. In the skeletal survey, a short first metacarpal was apparent. The ossific nuclei of the patella was absent, a normal feature at this age.

Targeted sequencing of *SLC26A2* (*DTDST*) identified the recurrent pathogenic variant c.835C>T (p.Arg279Trp) in homozygosity, confirming the diagnosis of rMED. Genetic counselling was performed. Clubfoot relapse was treated with repeated Ponseti manipulation and casting followed by percutaneous Achilles tenotomy.

Discussion
Clubfoot are not usually seen in MED caused by autosomal dominant forms (*COMP* or *COL9A2* mutations). *SLC26A2* is the only gene in which pathogenic variants are known to cause EDM4/rMED. Since p.Arg279Trp variant appears to be the most frequent *SLC26A2* in Europe (non-Finnish), homozygotes may not be particularly rare. This condition may be underdiagnosed. Wide clinical variability makes prognosis difficult to establish, especially in this young child who besides the club foot has already short stature (-2.85SD). The diagnostic value of the double layered patella and, perhaps more importantly, of club foot remains to be established.

Conclusion
Recessive Multiple Epiphyseal Dysplasia is usually diagnosed in older stages of childhood. Deformities, joint pain, double-layered patella or degenerative findings are not present on early ages. Atypical Clubfoot and early clubfoot relapse should challenge an initial diagnosis of idiopathic clubfoot and trigger further investigation.

C17. Recessive multiple epiphyseal dysplasia case series: same *SLC26A2* variant, different clinical features

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Abstract

Introduction: *SLC26A2* pathogenic variants cause a spectrum of autossomal recessive skeletal dysplasias: from lethal achondrogenesis type 1B and atelosteogenesis type 2, to classical diastrophic dysplasia and, at the milder end, recessive multiple epiphyseal dysplasia (rMED or EDM4). rMED is characterized by joint pain, usually at hips or knees and related to the epiphyseal dysplasia, hands and feet anomalies, and less frequently other findings such clubfoot, cystic ear swelling, scoliosis, short stature, and double-layered patella. The most common variant in non-Finnish populations is p.Arg279Trp, which when in homozygosity leads to rMED. Interestingly and contrary to the literature, in our centre rMED has been the most common form of MED identified. We describe here all cases diagnosed between 2015 and 2022.

Case Series: We characterized clinically, radiologically, and molecularly five unrelated patients with *SLC26A2* rMED, one male and four females, with present age range 18 months to 58 years. Age at diagnosis varied from 15 months to 56 years. Genotype was the same in all: homozygosity for the recurrent *SLC26A2* p.Arg279Trp variant. Two were diagnosed by targeted testing while the others were by a skeletal dysplasia large multigene panel. Four patients had joint pain and all had brachydactyly. Three patients had short stature, one of them with an adult height of -5.2SD. Two patients had mesomelia, one with Madelung deformity. One patient had bilateral clubfoot and cystic ear swelling.

Discussion: The present case series illustrates well and widens the clinical heterogeneity known in rMED. Surprisingly some patients had more severe phenotype than expected, raising the hypothesis of other concomitant predisposition factors, and making it difficult to establish a prognosis. In Portugal, this condition may be more frequent than expected.

C18. *CANT1*-related skeletal dysplasia: case report of two unrelated Portuguese patients with Desbuquois dysplasia, Kim variant / MED7

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Introduction: Desbuquois dysplasia (DD) is a severe autosomal recessive osteochondrodysplasia belonging to the multiple dislocation group. It is phenotypically characterized by micromelic short stature, joint laxity with multiple dislocations at birth, specific radiographic findings and facial dysmorphisms. It is clinically and genetically heterogeneous. At least three subtypes are recognized according to distinctive metacarpal and phalange alterations: DD type 1, DD type 2, and the Kim variant. Biallelic pathogenic variants in *CANT1* (calcium activated nucleotidase 1), involved in proteoglycan metabolism, have been identified in a subset of patients with not only DD type 1, but also DD type 2, DD Kim variant and multiple epiphyseal dysplasia type 7 (MED7).

Case reports: Here we report two unrelated Portuguese female individuals with the diagnosis of DD Kim variant / MED7. Patient 1, first child of non-consanguineous parents, was first observed by our team at the age of 12 months, had prenatal onset proportionate short stature, congenital left hip dysplasia treated with Pavlic harness, and advanced carpal bone age. She sat at 10 months and independent walked at 14 months. At last evaluation at 3 years and 4 months, height was 86.9cm (-2.84SD). Hearing tests and sleep study were normal. Patient 2 had consanguineous parents and two other affected sibs. She was first observed by our team at 65 years of age and had severe short stature (1.27m, -5.6SD), microcephaly (51cm, -3.2SD), possible history of hip dislocation at birth, severe joint pain, and previous orthopaedical interventions: right total hip replacement, revised, and right total knee replacement. In both patients, one at the age of 23 months and the other at 66 years, for a skeletal dysplasia NGS panel identified the recurrent *CANT1* pathogenic variant c.676G>A p.(Val226Met) in the homozygous state.

Discussion: This particular *CANT1* variant has been previously reported in several patients, once classified as DD Kim variant, others as MED7. Most likely these classifications reflect the presence or not of dislocations at birth and different ages at diagnosis, but certainly the prognosis is similar. The description of these two patients, at very distinct ages, illustrate well the phenotypic spectrum related to this variant and increase the knowledge on its the natural history. Precise diagnoses in these families were crucial to allow accurate genetic counselling.

C19. *Ectopia cordis*: historical case report of a rare congenital heart and sternal defect found in the Coimbra University

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Abstract text:

Ectopia cordis (EC) is an extremely rare congenital condition, characterized by complete or partial location of the heart outside the thoracic cavity, frequently presenting sternal abnormalities. EC is described nowadays as a life-threatening anomaly requiring prompt medical and surgical interventions. Although the first use of the term EC dates back to the 18th century the scant historical literature available precludes a comprehensive knowledge of its paleoepidemiology, sociocultural and biomedical relevance over time.

By combining historical, anthropological, and medical perspectives, this presentation aims to describe an EC case from 19th century, which is to our knowledge the first reported in Portugal. Three archival sources were consulted: 1) Coimbra University Hospitals admission records and inpatient medical records (*papeleta*); 2) Coimbra Municipality Cemetery (Conchada) burial records; 3) Caparrosa parish (Tondela, Viseu) baptism records.

The historical case report here presented refers to a 15-year-old shepherd male, born in Caparrosa, Tondela, inpatient of the Coimbra University Hospitals between 1882 and 1885. The diagnosis at admission was "ectopic heart over the midline and adherent to the skin; large sternal cleft" (*ectopia do coração collocado na linha media e adherente à pelle; larga fenda do esterno*). This long survival of an EC patient in the 19th century is remarkable. The diagnosis, comorbidities, prescribed diet and treatments during the internment, as well as the circumstances and cause of death, will be explored in order to unveil the underlying sociocultural context of this patient and his relevance for the local and global history of rare congenital diseases.

C20. Management of multiple orthopaedic problems in a patient with recessive Larsen Syndrome

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Introduction

Bone dysplasias with multiple dislocations are a group of different diseases, with distinct natural histories, prognosis, and genetic counselling implications. CHST3-related skeletal dysplasia, also known as recessive Larsen syndrome, is characterized by hyperlaxity, facial dysmorphisms and bone and joint abnormalities that worsen over time. Joint dislocations, most often affecting the knees, hips, and elbows, are present at birth. Distinct from AD Larsen syndrome, severe short stature with kyphosis and trunk shortening develops during childhood; and cardiac valvular disease may appear. Early diagnosis is important, so that the patient can benefit from a multidisciplinary adequate management, to prevent severe morbidity and improve quality-of-life.

Methods

Case presentation of a child with CHST3 deficiency and multiple joint dislocations. In the first month of life, she underwent gentle manipulation and casting for her bilateral knee dislocations and foot deformity. After 5 casts, a 90º of knee flexion was obtained and an orthosis was applied, with difficulties in compliance. At 10 months of age, x-ray revealed a persistent right knee and hip dislocation, and the patient was proposed for surgical treatment. She then suffered several respiratory infections and was operated at 23 months of age. In the same surgical time, we performed and open reduction of the hip with 2.5cm shortening of right femur and Dega acetabuloplasty and an open reduction of the right knee with a V-Y lengthening of quadriceps tendon, extra-articular reconstruction of anterior and posterior cruciate ligaments using ispsilateral autologous fascia lata and iliotibial band. The patient was immobilized with a unilateral spica cast after surgery for 8 weeks. An articulated knee orthosis was applied after cast removal.

At 5 years of age, and despite she had no spine symptoms, the cervical spine was screened for instability, following what is recommended for this syndrome. A radiograph identified odontoid apophysis hypoplasia and C2-C4 cervical kyphosis. Dynamic radiographs, CT and MRI, confirmed cervical instability. The patient underwent C1-C2 posterior arthrodesis at 7 years of age.

Results

After 7 years, the girl has a subtle limping gait; 130º left knee flexion and 90º right knee flexion, 0º bilateral knee extension; symmetrical hip mobility. X-rays show reduction of both joints. Regarding the cervical spine, at 20 months postoperatively, she has no complaints; control x-rays with good alignment and well positioned implants.

Conclusion

Recessive Larsen syndrome, caused by CHST3 deficiency, is rare and its diagnosis is challenging. The presence of a bone dysplasia associated with multiple congenital dislocations in a child with normal cognitive development should raise the suspicion of this group of disorders.

The treatment of these children is based on surgical reduction of the affected joints, when clinically and functionally justified. Surgical reduction of the hip and knee in a single surgical time is effective and safe.

Knowledge of the natural history of this pathology is essential and clinicians should have a high level of suspicion for cervical instability, as it is mostly asymptomatic and can be associated with catastrophic consequences, reason for which surgical treatment is advised.

C21. Bilateral Knee Osteochondritis Dissecans within an Aggrecanopathy Case

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Introduction

Aggrecan is a chondroitin sulphated proteoglycan, an essential component of the cartilage growth plate, encoded by the *ACAN* gene. Heterozygous *ACAN* mutations have been associated with a broad spectrum of autosomal dominant short stature phenotypes, from isolated to associated to skeletal abnormalities including a mild form of spondyloepiphyseal dysplasia and/or recurrent osteochondritis dissecans (OCD). Biallelic/recessive variants cause a rarer severe form of spondyloepimetaphyseal dysplasia. This group of disorders is called Aggrecanopathies. OCD is a rare disease for which no consensus has been established on the best course of treatment. We present a case of bilateral knee OCD caused by a pathogenic heterozygous variant in the gene *ACAN*.

Material and Results

14-year-old female, referred from another hospital to endocrinology due to short stature of prenatal onset. Her height and weight were 134cm (-4.1SD) and 38,7kg, respectively and she showed predominant shortening of the trunk compared to the limbs and hypertelorism. Hyposthesia of the left limbs and muscle weakness of the left inferior limb were present, accompanying gait claudication and a left knee flexus of 10º. She was then referred to Genetics, Orthopedics and Neurology consultations due to short stature and occasional left thigh pain. Previous laboratory tests and hypophysis' CT showed no significant findings. Brain MRI and hip radiographs were normal; spine radiographs showed dextroscoliosis (T5-T10 Cobb 19º); Knee radiographs and MRI revealed bilateral internal condyle OCD. Sports avoidance was recommended. Next generation sequencing of a panel of genes associated to skeletal dysplasias identified a pathogenic heterozygous frameshif mutation in ACAN gene c2328del p.(Ala777Glnfs*33) and confirmed the diagnosis. Currently, the patient has no significant bilateral knee pain, maintains, with a slight improvement, the OCD radiographic findings and is being followed-up by a multidisciplinary team.

Conclusion

There is a clear link between mutated *ACAN* and short stature, early onset osteoarthritis and skeletal abnormalities. The association with OCD, although less frequent, has been described (MIM##165800) and when identified in a person with short stature should raise this diagnostic suspicion.

Aggrecanopathies should be considered in children with short stature, poor growth spurt and joint involvement and a multidisciplinary approach is crucial for the correct diagnosis and treatment.

The evidence supporting one particular treatment strategy for OCD related to *ACAN* mutations is still very weak.

At the long-term, early onset osteoarthritis is likely to be the main concern. Reaching a precise