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Flash recherche : il s'agit d'une newsletter dédiée aux travaux de recherche, études cliniques, appels à projets...en lien avec la filière.

Si vous souhaitez proposer un thème, une étude, contactez : *arnaud.peramo@aphp.fr*

Adult rheumatologic features, treatment and complications of X-linked hypophosphatemia

IINSERM UMR 1153 - METHODS - Méthodes de l'évaluation thérapeutique des maladies chroniques

X-linked hypophosphatemia (XLH) is a rare genetic phosphate disorder caused mainly by PHEX mutations. Unlike for children, knowledge of the disease's manifestations in adults is limited. Musculoskeletal symptoms are the main feature of the disease in young adults associated with a heavy burden on patients' life. They include fractures and pseudofractures, pain, joint stiffness, osteoarthritis, enthesopathies, and muscle weakness, eventually leading to impaired quality of life. Conventional treatment with phosphate supplements and vitamin D analogs is indicated in symptomatic patients. Appropriate rehabilitation is also a key to the management of the disease to improve physical function and decrease pain, stiffness, and fatigue. Regarding the incidence and consequences of musculoskeletal features in XLH, all patients should be assessed by a bone disease specialist and, if necessary, managed by a multidisciplinary team.

Lire l'article

Pyridazinone derivatives limit osteosarcoma-cells growth in vitro and in vivo

EA4691 BIOS - Biomatériaux et inflammation en site osseux

Osteosarcoma is a rare primary bone cancer that mostly affects children and young adults. Current therapeutic approaches consist of combining surgery and chemotherapy but remain unfortunately insufficient to avoid relapse and metastases. Progress in terms of patient survival has remained the same for 30 years. In this study, novel pyridazinone derivatives have been evaluated as potential anti-osteosarcoma therapeutics because of their anti-type 4 phosphodiesterase activity, which modulates the survival of several other cancer cells. By using five-four human and one murine osteosarcoma-cell lines, we demonstrated differential cytotoxic effects of four pyridazinone scaffold-based compounds (mitochondrial activity and DNA quantification). Proapoptotic (annexin V positive cells and caspase-3 activity), anti-proliferative (EdU integration) and anti-migratory effects (scratch test assay) were also observed. Owing to their cytotoxic activity in in vitro conditions and their ability to limit tumor growth in a murine orthotopic osteosarcoma model, our data suggest that these pyridazinone derivatives might be hit-candidates to develop new therapeutic strategies against osteosarcoma.

Lire l'article

Oral Health-Related quality of life in patients with X-linked hypophosphatemia: a qualitative exploration

INSERM 1185 - Endocrinologie et Physiopathologie et EA2496 - Pathologies, imagerie et biothérapies oro-faciales

Introduction: X-linked hypophosphatemia (XLH) is a rare, hereditary, and lifelong phosphate wasting disorder characterized by rickets in childhood and impaired teeth mineralization. In the oral cavity, spontaneous abscesses can often occur without any clinical signs of alteration of the causal tooth. The objective of our study was to evaluate the oral care pathway and the oral health-related quality of life (OHRQoL) of patients followed in an expert oral medicine department located within a Parisian hospital and working in close collaboration with an endocrinology department expert in this pathology.

Methods: This study employed a qualitative descriptive design including

semi-structured interviews using guiding themes.

Results: Twenty-one patients were included in the study. The topics brought up exceeded the initial objectives as the patients mostly addressed the alteration of their oral health-related and general quality of life; a very chaotic oral health care pathway with oral health professionals not aware of their pathology; consequences on their social, professional, and school integration. Patients declared the importance of having a multidisciplinary team around them, including medical and dental professionals.

Conclusions: The variety of manifestations in patients with XLH necessitates a high coordination of multidisciplinary patient care to optimize quality of life and reduce disease burden. Oral health care pathways are very chaotic for patients who have difficulty finding professionals with sufficient knowledge of the disease. OHRQoL is therefore diminished. This situation improves when patients enter a coordinated care network.

Lire l'article

Imaging patterns in pediatric hypophosphatasia

INSERM 1185 - Endocrinologie et Physiopathologie

Hypophosphatasia is a rare genetic disorder of calcium and phosphate metabolism due to ALPL gene mutations, which leads to abnormal mineralization of the bones and teeth. Hypophosphatasia is characterized by low serum alkaline phosphatase activity and a number of clinical signs, including failure to thrive, bone pain and dental issues. The diagnosis is suspected based on clinical, laboratory and imaging findings and confirmed by genetic testing. Diagnosis in children is often delayed due to a lack of disease awareness, despite specific imaging findings that are a cornerstone of the diagnosis. The recent approval of enzyme replacement therapy (bone-targeted recombinant tissue nonspecific alkaline phosphatase) has given imaging an important role in monitoring treatment efficacy. The aim of this pictorial essay is to review the imaging features of hypophosphatasia at diagnosis and during follow-up, including whole-body magnetic resonance imaging patterns.

Lire l'article

Drug-Related Hypercalcemia

INSERM 1185 - Endocrinologie et Physiopathologie et INSERM UMR S1138/CNRS ERL8228 Physiologie Rénale et tubulopathies

This review focuses on the commonly prescribed medicaments that can be responsible for hypercalcemia, considering the prevalence, the predominant pathophysiological mechanisms, and the optimal medical management of each drug-induced hypercalcemia. Vitamin D supplements and 1α-hydroxylated vitamin D analogues increase intestinal calcium absorption, renal calcium reabsorption as well as bone resorption. In patients with hypoparathyroidism receiving recombinant human PTH, transient hypercalcemia can occur because of overtreatment, usually during acute illness. Thiazide-induced hypercalcemia is mainly explained by enhanced renal proximal calcium reabsorption, changing preexistent asymptomatic normocalcemic or intermittently hypercalcemic hyperparathyroidism into the classic hypercalcemic hyperparathyroidism. Lithium causes hypercalcemia mainly by drug-induced hyperparathyroidism.

Lire l'article

WNT11, a new gene associated with early-onset osteoporosis, is required for osteoblastogenesis

INSERM UMR 1132 - BIOSCAR - Biologie de l'os et du cartilage et UMR 1301 (Inserm) / UMR 5070 (CNRS) Geroscience and rejuvenation research center - RESTORE

Monogenic early-onset osteoporosis (EOOP) is a rare disease defined by low bone mineral density (BMD) that results in increased risk of fracture in children and young adults. Although several causative genes have been identified, some of the EOOP causation remains unresolved. Whole-exome sequencing revealed a de novo heterozygous loss-of-function mutation in WNT11 (NM_004626.2:c.677_678dup p.Leu227Glyfs*22) in a 4-year-old boy with low BMD and fractures. We identified two heterozygous WNT11 missense variants (NM_004626.2:c.217G > A p.Ala73Thr) and (NM_004626.2:c.865G > A p.Val289Met) in a 51-year-old woman and in a 61-year-old woman respectively, both with bone fragility. U2OS cells with heterozygous WNT11 mutation (NM_004626.2:c.690_721delfs*40) generated by CRISPR-Cas9 showed reduced cell proliferation (30%) and osteoblast differentiation (80%) as compared with wild-type U2OS cells. The expression of genes in the Wnt canonical and non-canonical pathways was inhibited in these mutant cells, but recombinant WNT11 treatment rescued the expression of Wnt pathway target genes. Furthermore, the expression of RSPO2, a WNT11 target involved in bone cell differentiation, and its receptor LGR5, was decreased in WNT11 mutant cells. Treatment with WNT5A and WNT11 recombinant

proteins reversed LGR5 expression, but WNT3A recombinant protein treatment had no effect on LGR5 expression in mutant cells. Moreover, treatment with recombinant RSPO2 but not WNT11 or WNT3A activated the canonical pathway in mutant cells. In conclusion, we have identified WNT11 as a new gene responsible for EOOP, with loss-of-function variant inhibiting bone formation via Wnt canonical and non-canonical pathways. WNT11 may activate Wnt signaling by inducing the RSPO2-LGR5 complex via the non-canonical Wnt pathway.

Lire l'article

Peripheral Blood Mononuclear Cells (PBMCs) to Dissect the Underlying Mechanisms of Bone Disease in Chronic Kidney Disease and Rare Renal Diseases

INSERM UMR 1033 - Lysophospholipides et physiopathologie osseuse

Purpose of review: To describe the methods that can be used to obtain functional and mature osteoclasts from peripheral blood mononuclear cells (PBMCs) and report the data obtained with this model in two peculiar diseases, namely pediatric chronic kidney disease-associated mineral and bone disorders (CKD-MBD) and nephropathic cystinosis. To discuss future research possibilities in the field.

Recent findings: Bone tissue undergoes continuous remodeling throughout life to maintain bone architecture; it involves two processes: bone formation and bone resorption with the coordinated activity of osteoblasts, osteoclasts, and osteocytes. Animal models fail to fully explain human bone pathophysiology during chronic kidney disease, mainly due to interspecies differences. The development of in vitro models has permitted to mimic human bone-related diseases as an alternative to in vivo models. Since 1997, osteoclasts have been generated in cell cultures, notably when culturing PBMCs with specific growth factors and cytokines (i.e., M-CSF and RANK-L), without the need for osteoblasts or stromal cells. These models may improve the global understanding of bone pathophysiology. They can be been used not only to evaluate the direct effects of cytokines, hormones, cells, or drugs on bone remodeling during CKD-MBD, but also in peculiar genetic renal diseases inducing specific bone impairment.

Lire l'article

Osteogenesis Imperfecta: characterization of fractures during pregnancy and post-partum

INSERM UMR 1163 - IMAGINE - Bases moléculaires et physiopathologiques des ostéochondrodysplasies ; INSERM UMR 1132 - BIOSCAR - Biologie de l'os et du cartilage ; EA4490 -Marrow adiposity and Bone Laboratory ; INSERM UMR 1291 - UMR5051 CPTP - Mécanismes moléculaires de la croissance, de l'ostéogenèse et de l'ostéolyse, biothérapies

Background: Pregnancy and breastfeeding are associated with bone density loss. Fracture occurrence during pregnancy and post-partum, and its determinants, remain poorly known in Osteogenesis Imperfecta (OI). The aim of this study was to characterize fractures that occurred during pregnancy and post-partum in OI patients.

Results: We conducted a retrospective multicentric study including a total of 50 previously pregnant OI women from 10 Bone Centers in France. Among these patients, 12 (24%) patients experienced fractures during pregnancy or in the 6 months following delivery, and 38 (76%) did not experience any fracture. The most frequent localizations were: proximal femur (25%), spine (25%), distal femur (12.5%), and pelvis (12.5%). Fractures during pregnancy occurred during the third trimester and post-partum fractures occurred with a mean delay of 2 months following delivery. No fractures occurred during childbirth. We next compared the 12 patients with pregnancy or post-partum fractures with the 38 patients without fractures. Mean age at pregnancy was 32.7 ± 3.1 years-old in the fractured group, vs 29.3 ± 5.0 years-old in the non-fractured group ($p = 0.002$). Breastfeeding was reported in 85.7% of patients in the fractured group, vs 47.1% in the non-fractured group ($p = 0.03$). All patients with post-partum fractures were breastfeeding. Bone mineral density was significantly lower in patients with pregnancy-related fractures compared with other patients: spine Z-score - 2.9 ± 1.6DS vs - 1.5 ± 1.7DS ($p = 0.03$), and total hip Z-score - 2.0 ± 0.7DS vs - 0.5 ± 1.4DS ($p = 0.04$). At least one osteoporosis-inducing risk factor or disease other than OI was identified in 81.8% vs 58.6% of fractured vs non-fractured patients (not significant). Fracture during pregnancy or post-partum was not associated with the severity of OI. Bisphosphonates before pregnancy were reported in 16.7% and 21.1% of patients with pregnancy-related fractures and non-fractured patients, respectively (not significant).

Conclusions: OI management during pregnancy and post-partum should aim for optimal control of modifiable osteoporosis risk factors, particularly in

patients with low BMD. Breastfeeding should be avoided.

Lire l'article

📅 Appel à projets

Impulsion à la recherche

L'appel à projets OSCAR est destiné à soutenir la recherche fondamentale, translationnelle, clinique et en sciences humaines et sociales relative aux maladies rares de la filière et à leur prise en charge.

Vous avez jusqu'au **30 avril 2022** pour déposer votre dossier à Arnaud PERAMO.

Plus d'information

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Retrouvez le **Pr Justine Bacchetta** qui vous parlera du métabolisme minéral de l'enfant FGF23.

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