Janvier 2022

Flash recherche

de la filière Oscar

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

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Geleophysic and acromicric dysplasias: natural history, genotype-phenotype correlations, and management guidelines from 38 cases

INSERM UMR 1163 - IMAGINE - Bases moléculaires et physiopathologiques des ostéochondrodysplasies

Purpose: Geleophysic dysplasia (GD) and acromicric dysplasia (AD) are characterized by short stature, short extremities, and progressive joint limitation. In GD, cardiorespiratory involvement can result in poor prognosis. Dominant variants in the FBN1 and LTBP3 genes are responsible for AD or GD, whereas recessive variants in the ADAMTSL2 gene are responsible for GD only. The aim of this study was to define the natural history of these disorders and to establish genotype-phenotype correlations.

Methods: This monocentric retrospective study was conducted between January 2008 and December 2018 in a pediatric tertiary care center and included patients with AD or GD with identified variants (FBN1, LTBP3, or ADAMTSL2).

Results: Twenty-two patients with GD (12 ADAMTSL2, 8 FBN1, 2 LTBP3) and 16 patients with AD (15 FBN1, 1 LTBP3) were included. Early death occurred in eight GD and one AD. Among GD patients, 68% presented with heart valve disease and 25% developed upper airway obstruction. No AD patient developed life-threatening cardiorespiratory issues. A greater proportion of patients with either a FBN1 cysteine variant or ADAMTSL2 variants had a poor outcome.

Conclusion: GD and AD are progressive multisystemic disorders with life-threatening complications associated with specific genotype. A careful multidisciplinary follow-up is needed.

Lire l'article

Bisphosphonates for the treatment of fibrous dysplasia of bone

INSERM UMR 1033 - Physiopathologie, diagnostic et traitement des affections musculosquelettiques

Introduction: Fibrous dysplasia of bone (FD) is a rare congenital bone disease, due to a somatic mutation of GNAS. This mutation results in a defect of osteoblast differentiation and mineralization and also an increase in bone resorption by large active osteoclasts. Bone pain is present in half of patients and is the main determinant of quality of life of patients with FD. Bisphosphonates are known to reduce bone pain and reduce the risk of fracture in patients with bone metastases or Paget's disease. Bisphosphonates may have similar effects in FD. In this article, we have reviewed the therapeutic potential of bisphosphonates to reduce bone pain due to FD, improve bone strength and reduce the occurrence of fracture.

Material and methods: We have reviewed 234 articles examining the effect of bisphosphonates on FD/McCune Albright Syndrome with no date limit, in PubMed and selected the articles with highest quality of methodology.

Results: Pamidronate therapy significantly decreased bone pain and bone resorption (urinary NTX, urinary and serum CTX). Pamidronate may improve radiological lesions of FD patients (filling of osteolytic lesion and/or cortical thickening). This data with intravenous pamidronate, however, has been obtained from observational studies and no randomized controlled trial is available. Randomized placebo-controlled trials of oral bisphosphonates (alendronate or risedronate) have failed to demonstrate a significant decrease in bone pain over placebo. Several studies including one

randomized controlled trial have shown an increase in bone mineral density (BMD) at FD sites with oral and intravenous bisphosphonate treatment. No effect on occurrence of fracture has been reported.

Conclusion: In conclusion, intravenous bisphosphonates may be proposed to treat persistent, moderate to severe bone pain of FD, e.g., according to the guidelines from the FD/MAS International Consortium. Oral bisphosphonates should not be used in this indication.

Lire l'article

Utility of genetic testing for prenatal presentations of hypophosphatasia

INSERM UMR 1291 - UMR5051 CPTP - Mécanismes moléculaires de la croissance, de l'ostéogenèse et de l'ostéolyse, biothérapies

Hypophosphatasia (HPP) is a rare inherited disease affecting bone and dental mineralization due to loss-of-function mutations in the ALPL gene encoding the tissue nonspecific alkaline phosphatase (TNSALP). Prenatal benign HPP (PB HPP) is a rare form of HPP characterized by in utero skeletal manifestations that progressively improve during pregnancy but often still leave symptoms after birth. Because the prenatal context limits the diagnostic tools, the main difficulty for clinicians is to distinguish PB HPP from perinatal lethal HPP, the most severe form of HPP. We previously attempted to improve genotype phenotype correlation with the help of a new classification of variants based on functional testing.
Among 46 perinatal cases detected in utero or in the neonatal period for whose ALPL variants could be classified, imaging alone was thought to clearly diagnose severe lethal HPP in 35 cases, while in 11 cases, imaging abnormalities could not distinguish between perinatal lethal and BP HPP.
We show here that our classification of ALPL variants may improve the ability to distinguish between perinatal lethal and PB HPP in utero.

Lire l'article

Lumbar spinal stenosis and disc alterations affect the upper lumbar spine in adults with achondroplasia

INSERM UMR 1132 - BIOSCAR - Biologie de l'os et du cartilage

In achondroplasia, lumbar spinal stenosis arises from congenital dysplasia and acquired degenerative changes. We here aimed to describe the changes of the lumbar spinal canal and intervertebral disc in adults.
We included 18 adults (age ≥ 18 years) with achondroplasia and lumbar spinal stenosis. Radiographs were used to analyze spinal-pelvic angles. Antero-posterior diameter of the spinal canal and the grade of disc degeneration were measured by MRI. Antero-posterior diameters of the spinal canal differed by spinal level ($P < 0.05$), with lower values observed at T12-L1, L1-2 and L2-3. Degrees of disc degeneration differed by intervertebral level, with higher degrees observed at L1-2, L2-3 and L3-4.
A significant correlation was found between disc degeneration and thoraco-lumbar kyphosis at L2-3, between antero-posterior diameter of the spinal canal and lumbar lordosis at T12-L1 and L2-3, and between antero-posterior diameter of the spinal canal and thoraco-lumbar kyphosis at L1-2.
Unlike the general population, spinal stenosis and disc degeneration involve the upper part of the lumbar spine in adults with achondroplasia, associated with thoraco-lumbar kyphosis and loss of lumbar lordosis.

Lire l'article

A novel familial PHP1B variant with incomplete loss-of-methylation at GNAS-A/B and enhanced methylation at GNAS-AS2

INSERM 1185 - Endocrinologie et Physiopathologie

Context: Pseudohypoparathyroidism type 1B (PHP1B), also referred to as inactivating PTH/PTHrP Signaling Disorder (iPPSD), is characterized by proximal renal tubular resistance to parathyroid hormone (PTH) leading to hypocalcemia, hyperphosphatemia and elevated PTH values. Autosomal dominant PHP1B (AD-PHP1B) with loss-of-methylation at the maternal GNAS A/B:TSS-DMR (transcription start site-differentially methylated region) alone can be caused by maternal deletions involving STX16.

Objectives: Characterize a previously not reported AD-PHP1B family with loss-of-methylation at GNAS A/B:TSS-DMR, but without evidence for a STX16 deletion on the maternal allele and assess GNAS-AS2:TSS-DMR methylation.
Patients and methods: DNAs from 24 patients and 10 controls were investigated. AD-PHP1B patients without STX16 deletion from a single family (n=3), AD-PHP1B patients with STX16 deletion (n=9), sporPHP1B (n=10), unaffected controls (n=10), patUPD20 (n=1), and matUPD20 (n=1). Methylation and copy number analyses were performed by pyrosequencing,

MS-MPLA, and MLPA, respectively.

Results: Molecular cloning of PCR-amplified, bisulfite-treated genomic DNA from healthy controls revealed evidence for two distinct GNAS-AS2:TSS-DMR subdomains, named AS2-1 and AS2-2, which showed 16.0±2.3% and 31.0±2.2% methylation, respectively. DNA from affected members of a previously not reported AD-PHP1B family without the known genetic defects revealed incomplete LOM (loss-of-methylation) at GNAS A/B:TSS-DMR, normal methylation at the three well-established maternal and paternal DMRs, and, surprisingly, increased methylation at AS2-1 (32.9±3.5%), but not at AS2-2 (30.5±2.9%).

Conclusion: The distinct methylation changes at the novel GNAS-AS2:TSS-DMR will help characterize further different PHP1B/iPPSD3 variants and will guide the search for underlying genetic defects, which may provide novel insights into the mechanisms underlying GNAS methylation.

Lire l'article

Treatment on adult bone and joints in a murine model of X-Linked Hypophosphatemia

EA2496 - Pathologies, imagerie et biothérapies oro-faciales

X-linked hypophosphatemia (XLH) is the most common form of genetic rickets. Mainly diagnosed during childhood because of growth retardation and deformities of the lower limbs, the disease affects adults with early enthesopathies and joint structural damage that significantly alter patient quality of life.
The conventional treatment, based on phosphorus supplementation and active vitamin D analogs, is commonly administered from early childhood to the end of growth; unfortunately, it does not allow complete recovery from skeletal damage.Despite adequate treatment during childhood, bone and joint complications occur in adults and become a dominant feature in the natural history of the disease.
Our previous data showed that the Hyp mouse is a relevant model of XLH for studying early enthesophytes and joint structural damage. Here, we studied the effect of conventional treatment on the development of bone and joint alterations in this mouse model during growth and young adulthood. Mice were supplemented with oral phosphorus and calcitriol injections, following two timelines: (i) from weaning to 3 months of age and (ii) from 2 to 3 months to evaluate the effects of treatment on the development of early enthesophytes and joint alterations, and on changes in bone and joint deformities already present, respectively. We showed that early conventional treatment improved bone microarchitecture, and partially prevented bone and joint complications, but with no noticeable improvement in enthesophytes. In contrast, later administration had limited efficacy in ameliorating bone and joint alterations. Despite the improvement in bone microarchitecture, the conventional treatment, early or late, had no effect on osteoid accumulation.
Our data underline the usefulness of the Hyp murine model for preclinical studies on skeletal and extraskeletal

Keutel syndrome, a review of 50 years of literature

UMR 7365 - CNRS-Université de Lorraine, IMoPA

Le syndrome de Keutel est une maladie génétique autosomique récessive rare qui a été identifiée pour la première fois en 1971 et, près de 30 ans plus tard, attribuée à des mutations « perte de fonction » dans le gène codant pour la protéine matricielle Gla ou MGP.

Les patients atteints du syndrome de Keutel, généralement diagnostiqués pendant l'enfance, présentent des signes cliniques variés incluant des malformations des tissus squelettiques (hypoplasie de la face médiane, brachytéléphalangisme, ...) et d'anomalies cardiovasculaires (sténose de l'artère pulmonaire périphérique et dans certains cas calcification artérielle), ainsi qu'une perte auditive et un léger retard mental et de croissance.

Alors que les études sur les souris déficientes en Mgp, modèle murin du syndrome de Keutel, démontrent clairement que les calcifications ectopiques dans les tissus cartilagineux et vasculaires sont la cause principale de ces anomalies, les mécanismes expliquant comment, en conditions physiologiques, la MGP empêche la calcification anormale restent toujours mal compris.

Dans cette revue, les auteurs résument les résultats publiés au cours des 50 dernières années sur les rares cas rapportés atteints du syndrome de Keutel et présentent l'état actuel des connaissances physiopathologiques sur cette pathologie rare et moléculaires sur son gène responsable Mgp.

Lire l'article

lesions. Although the early conventional treatment is important for the improvement of bone microarchitecture, the persistence of osteomalacia implies seeking new therapeutic strategies, in particular anti-FGF23 approach, in order to optimize the treatment of XLH.

Lire l'article

Longitudinal Bone Loss Occurs at the Radius in CKD

INSERM UMR S1138/CNRS ERL8228 - Physiologie rénale et tubulopathies
INSERM UMR 1132 - BIOSCAR - Biologie de l'os et du cartilage

Introduction: Chronic kidney disease (CKD) exposes to an increased incidence of fragility fractures. International guidelines recommend performing bone mineral density (BMD) if the results will impact treatment decisions. It remains unknown where bone loss occurs and what would preclude the longitudinal loss in patients with CKD. Here, we aimed to investigate factors influencing BMD and to analyze the longitudinal BMD changes.

Methods: In the NephroTest cohort, we measured BMD at the femoral neck, total hip, lumbar spine, and proximal radius, together with circulating biomarkers and standardized measured glomerular filtration rate (mGFR) by 51Cr-EDTA in a subset of patients with CKD stage 1 to 5 followed during 4.3 ± 2.0 years. A linear mixed model explored the longitudinal bone loss and the relationship of associated factors with BMD changes. A total of 858 patients (mean age 58.9 ± 15.2 years) had at least 1 and 477 had at least 2 BMD measures.

Results: At baseline, cross-sectional analysis showed a significantly lower BMD at femoral neck and total hip and a significant higher serum parathyroid hormone (PTH) along with CKD stages. Baseline age, gender, tobacco, low body mass index (BMI), and high PTH levels were significantly associated with low BMD. Longitudinal analysis during the mean 4.3 years revealed a significant bone loss at the radius only. BMD changes at the femoral neck were associated with BMI, but not CKD stages or basal PTH levels. Conclusions: CKD is associated with low BMD and high PTH in the cross-sectional analysis. Longitudinal bone loss occurred at the proximal radius after 4.3 years.

Lire l'article

An Fgfr3-activating mutation in immature murine osteoblasts affects the appendicular and craniofacial skeleton

INSERM UMR1229 - Regenerative Medicine and Skeleton
INSERM UMR 1163 - IMAGINE - Bases moléculaires et physiopathologiques des ostéochondrodysplasies

Achondroplasia (ACH), the most common form of dwarfism, is caused by a missense mutation in the gene coding for fibroblast growth factor receptor 3 (FGFR3). The resulting increase in FGFR3 signaling perturbs the proliferation and differentiation of chondrocytes (CCs), alters the process of endochondral ossification and thus reduces bone elongation. Increased FGFR3 signaling in osteoblasts (OBs) might also contribute to bone anomalies in ACH. In the present study of a mouse model of ACH, we sought to determine whether FGFR3 overactivation in OBs leads to bone modifications. The model carries an Fgfr3-activating mutation (Fgfr3Y367C/+) that accurately mimics ACH; we targeted the

Mouse mutant phenotyping at scale reveals novel genes controlling bone mineral density

Présentation du Dr Yann Hérault - RDV de la recherche OSCAR

The genetic landscape of diseases associated with changes in bone mineral density (BMD), such as osteoporosis, is only partially understood.

Here, we explored data from 3,823 mutant mouse strains for BMD, a measure that is frequently altered in a range of bone pathologies, including osteoporosis.
A total of 200 genes were found to significantly affect BMD. This pool of BMD genes comprised 141 genes with previously unknown functions in bone biology and was complementary to pools derived from recent human studies. Nineteen of the 141 genes also caused skeletal abnormalities. Examination of the BMD genes in osteoclasts and osteoblasts underscored BMD pathways, including vesicle transport, in these cells and together with in silico bone turnover studies

mutation to either immature OBs and hypertrophic CCs or to mature OBs by using the Osx-cre and collagen 1α1 (2.3 kb Col1a1)-cre mouse strains, respectively.

We observed that Fgfr3 activation in immature OBs and hypertrophic CCs (Osx-Fgfr3) not only perturbed the hypertrophic cells of the growth plate (thus affecting long bone growth) but also led to osteopenia and low cortical thickness in long bones in adult (3-month-old) mice but not growing (3-week-old) mice. Importantly, craniofacial membranous bone defects were present in the adult mice. In contrast, activation of Fgfr3 in mature OBs (Col1-Fgfr3) had very limited effects on skeletal shape, size and micro-architecture. In vitro, we observed that Fgfr3 activation in immature OBs was associated with low mineralization activity. In conclusion, immature OBs appear to be affected by Fgfr3 overactivation, which might contribute to the bone modifications observed in ACH independently of CCs.

resulted in the prioritization of candidate genes for further investigation.

Overall, the results add novel pathophysiological and molecular insight into bone health and disease.

Lire l'article

Lire l'article

Neuromedin B promotes chondrocyte differentiation of mesenchymal stromal cells via calcineurin and calcium signaling

INSERM U1183 - IRMB - Cellules souches mésenchymateuses, niche et homéostasie tissulaire

Background: Articular cartilage is a complex tissue with poor healing capacities. Current approaches for cartilage repair based on mesenchymal stromal cells (MSCs) are often disappointing because of the lack of relevant differentiation factors that could drive MSC differentiation towards a stable mature chondrocyte phenotype.

Results: We used a large-scale transcriptomic approach to identify genes that are modulated at early stages of chondrogenic differentiation using the reference cartilage micropellet model. We identified several modulated genes and selected neuromedin B (NMB) as one of the early and transiently modulated genes. We found that the timely regulated increase of NMB was specific for chondrogenesis and not observed during osteogenesis or adipogenesis. Furthermore, NMB expression levels correlated with the differentiation capacity of MSCs and its inhibition resulted in impaired chondrogenic differentiation indicating that NMB is required for chondrogenesis. We further showed that NMB activated the calcineurin activity through a Ca2+-dependent signaling pathway.

Conclusion: NMB is a newly described chondroinductive bioactive factor that upregulates the key chondrogenic transcription factor Sox9 through the modulation of Ca2+ signaling pathway and calcineurin activity.

Lire l'article

Magnetic resonance imaging is a valuable tool to evaluate the therapeutic efficacy of burosumab in children with X-linked hypophosphatemia

INSERM 1185 - Endocrinologie et Physiopathologie, EA2496 - Pathologies, imagerie et biothérapies oro-faciales
INSERM UMR 1153 - METHODS - Méthodes de l'évaluation thérapeutique des maladies chroniques

Purpose: To examine the MRI diagnostic performance in the assessment of therapeutic response to burosumab in children with X-linked hypophosphatemia (XLH).

Design: Prospective longitudinal open cohort.

Patients: Seventeen children with XLH, average age of 10.2 ± 2.7 years, had a knee MRI at baseline and after 1 year of burosumab.

Intervention: Children received burosumab at an average dose of 1.4 ± 0.5

mg/kg during 1 year for the treatment of severe rickets (the target serum phosphate ≥ 1.2 mmol/L (≥3.7 mg/dL). The primary endpoint was the change from baseline to 12 months in rachitic lesions on knee MRI. Secondary endpoints were changes in biochemical parameters of phosphate and alkaline phosphatase (ALP).

Results: One year of treatment with burosumab significantly reduced radiological disease activity on knee MRI (by 44 ± 29% in the transverse extent of widening) which was accompanied by a significant reduction in biochemical activity, namely in serum ALP activity, by 28 ± 17%. Additionally, MRI parameters after 1 year of treatment with burosumab (the maximum width of medial physis at 12 months and the change from baseline in the maximum width of lateral physis) were associated with ALP activity at 12 months.

Conclusion: We suggest that MRI is a valuable and quantitative tool to evaluate the therapeutic response to burosumab. MRI could be an excellent alternative to standard bone radiographs for evaluation of the rachitic lesions in a clinical setting avoiding repeated exposition to ionizing radiation.

Lire l'article

📅 Appel à projets

Appel à communications

La filière OSCAR lance son premier **appel à communications** sur les maladies rares de l'os, du calcium et du cartilage et leur prise en charge pour la prochaine journée de la rechercher translationnelle du 30 juin 2022 : **plusieurs communications seront sélectionnées et pourront être présentées sous forme de posters.**

Pour postuler, un abstract et un court CV sont à envoyer à arnaud.peramo@aphp.fr avant le **6 février 2022**.

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Plus d'information

📣 Save the date

25 janvier 2022 : RDV de la Recherche

Participez à notre premier RDV de la Recherche de l'année, notre rendez-vous mensuel autour de thématiques scientifiques, le **mardi 25 janvier 2022** avec le Pr Valérie CORMIER DAIRE pour une présentation sur "*Un nouveau traitement pour l'achondroplasie*".

L'inscription est gratuite mais obligatoire.

Inscription

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31 mars 2022 : Symposium Outils diagnostiques

Programme à venir

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30 juin 2022 : Journée de la Recherche translationnelle

Programme à venir

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