Article:
Orlando, G., Clarke, S., Roy, M. et al. (5 more authors) (2021) Physical function and mobility in adults with X-linked hypophosphatemia. Bone Reports, 14. 101002. ISSN 2352-1872

https://doi.org/10.1016/j.bonr.2021.101002

transformation, of 9.5X7cm, weight=117grams (with liquid), =40grams (without liquid), wall thickness=0.3-0.7cm (with principal cells). Post-operatory symptomatic hypocalcemiaTCa=8.4mg/dL (N:8.5-10.2) with normal PTH=39pg/mL(N:15-65).

Conclusion(s): Particular aspect of the case: the rarity of GPTA of such dimensions, with cystic appearance. GPTA is functional but the presentation as an emergency is mostly related to the presence of a large neck tumor rather than PHP complicated with de novo osteoporosis. Complete cystic transformation probably follows the secretory activity of solid adenoma. The hemorrhagic shift seems spontaneous. Parathyroid tumors with rapid evolution and mass effect need to be differentiated from parathyroid carcinoma.

Key words: giant parathyroid adenoma, cyst, primary hyperparathyroidism, tumor, hypercalcemia

doi:10.1016/j.bonr.2021.100998

P187

Arnold Chiari malformation (ACM) in XLH: Rare but important complication of a rare disease

Zaineb Mohsin, Muhammad Kassim Javaid
Nuffield Orthopaedics Centre, Rheumatology, London, United Kingdom

Background/Introduction: X Linked hypophosphataemia (XLH) is a rare condition that typically causes musculoskeletal manifestations in adults. However, it is associated with serious neurological manifestations that are under recognized such as the Arnold-Chiari malformation.

Purpose: To highlight the need for a high index of suspicion for ACM which can have non-specific clinical features but can lead to considerable morbidity and mortality.

Methods: A 29 year old gentleman had severe X-Linked Hypophosphataemia. He was wheel-chair enabled from severe hip and back pain despite extensive orthopaedic interventions. An MRI of the c-spine at the age of 23 for severe headaches/ migraines, when he was diagnosed as suffering from an Arnold Chiari malformation and he was under annual neurosurgical follow up. He was diagnosed with obstructive sleep apnoea, attributed to his BMI of 36. At the age of 27, he was admitted to ITU with respiratory failure and pneumonia. Post discharge, he complained of dysphagia and diagnosed with bronchiectasis. Bilateral neuropathy of his hands was attributed to a post ITU syndrome.

Results: He was readmitted to ITU the following year for respiratory failure and septic shock presumed and unfortunately succumbed to his illness. The unifying diagnosis for his sleep apnoea, aspiration with secondary bronchiectasis, dysphagia and respiratory failure is ACM.

Conclusion(s): ACM in XLH could be explained by calvarial thickening, decreased size of the posterior fossa and sagittal synostosis. A neurologic cause should be considered for adults with XLH who develop respiratory or swallowing symptoms, even in the absence of prominent signs and symptoms. MRI is crucial in diagnosing ACM. Screening questions for ACM condition should be part of the routine followup checklist.

doi:10.1016/j.bonr.2021.101000

P189

A rare case of thoracic Gorham-Stout disease presenting with recurrent pleural effusions

Zaineb Mohsin[a], Karen Partington[b], James Teh[b], Najib Rahman[c], Muhammad Kassim Javaid[a]
[a]*Nuffield Orthopaedics Centre, Rheumatology, London, United Kingdom*
[b]*Oxford University Hospitals NHS Trust, Radiology, London, United Kingdom*
[c]*Oxford University Hospitals NHS Trust, Respiratory Diseases, London, United Kingdom*

Background/Introduction: Gorham-Stout disease (GSD) is a rare complex lymphatic anomaly characterized by osteolysis. Thoracic involvement can be associated with a chylothorax, a poor prognostic sign with a mortality range of 33 to 53%.

Purpose: To present the clinical features of this disease when it affects the thorax and to highlight the importance of collaboration with international experts.

Methods: A 44-year-old woman gave a 10-year history of intermittent severe musculoskeletal pain of the neck and right shoulder lasting 1 to 4 weeks. Following investigations by orthopaedics for shoulder pain and neurology for neck pain, she was referred to complex pain clinics. She developed breathlessness with the pain attacks in 2020 and a chest x-ray showed a moderate right pleural effusion with incidental finding of missing right ribs 2-5. An MRI demonstrated C7, T1 and T2 and sternal involvement. Despite drainage of the pleural effusion, follow up imaging revealed re-accumulation of pleural fluid and minimal pericardial and left sided pleural effusions. The CA-125 was raised and extensive gynaecological investigations exclude malignancy. Bone profile including PINP, liver and renal function were normal. Pleural fluid was exudative without a chylothorax. The right pleural histopathology showed non-specific inflammation and mild fibrosis with negative immunohistochemistry for lymphatic vessels using D2-40.

Results: Following consultation with the LGDA medical advisory board 4 weekly zoledronic acid 4mg was started with a plan to add in sirolimus to reduce mTOR activity, thought be central to the pathogenesis.

Conclusion(s): GSD is a rare bone disease that can present differently according to the anatomical region involved. Management requires a multidisciplinary approach and collaboration with international experts with a wider experience to plan effective treatment.

doi:10.1016/j.bonr.2021.101001

P191

Physical function and mobility in adults with X-linked hypophosphatemia

Giorgio Orlando[a], Shane Clarke[b], Matthew Roy[b], Robin Lachmann[c], Jennifer Walsh[d], Marian Schini[d], Javaid Kassim[e], Alex Ireland[a]
[a]*Manchester Metropolitan University, Musculoskeletal Science and Sports Medicine Research Centre- Department of Life Sciences, Manchester, United Kingdom*
[b]*University Hospitals Bristol, Department of Rheumatology, Bristol, United Kingdom*
[c]*Charles Dent Metabolic Unit, University College London Hospitals, London, United Kingdom*
[d]*University of Sheffield, Department of Oncology and Metabolism, Sheffield, United Kingdom*
[e]*University of Oxford, Nuffield Department of Orthopaedics- Rheumatology and Musculoskeletal Sciences, Oxford, United Kingdom*

Background/Introduction: X-linked Hypophosphatemia (XLH) is a rare genetic disorder affecting phosphate metabolism. Whilst muscle weakness has been reported in adults with XLH, there is little data describing detailed physical function.

Purpose: We examined upper and lower limb function and fitness in UK adults with XLH and assessed the relationships between physical function and mobility.

Methods: Adults with XLH were recruited as part of an ongoing UK-based prospective cohort study, the RUDY Study. Participants underwent a clinical visit and physical examination. This included grip strength and jump power assessed by mechanography, six-minute walk test (6MWT) and short physical performance battery (SPPB). Scores were compared with existing age and sex-specific normative data using t-test, whereas correlations among outcomes were processed using Pearson's correlation coefficient.

Results: Twenty-nine adults with XLH (15 males and 14 females), with a mean age of 46.8±15.8 years were enrolled to the study. Grip strength was 27% lower ($p=0.005$) and jump power 63% lower in individuals with XLH than normative values ($p<0.0001$), with greater deficits evident in the lower than upper body ($p=0.003$). Aerobic fitness was 42% lower in XLH individuals when compared to reference values ($p<0.0001$). Mean SPPB score was 8.6±3.3, with 14/29 individuals having a score of <10 indicating impaired mobility. Univariate correlations revealed that handgrip strength ($r=0.591$, $p<0.001$), jump power ($r=0.630$, $p<0.001$) and aerobic fitness ($r=0.739$, $p<0.0001$) were all highly correlated to mobility (SPPB).

Conclusion(s): Adults with XLH had weaker lower body power than other components of physical function. Upper and lower limb function and aerobic fitness were all strongly associated with impaired mobility in this population, which suggests that the origin of mobility deficits may be multifactorial. Further studies are required to understand underlying mechanisms, and to develop novel treatment approaches to improve physical function and mobility.

doi:10.1016/j.bonr.2021.101002

P193

Development of an observational registry for genetic hypophosphatemia and acquired renal phosphate wasting in The Netherlands: ORPHOS-NED

Ariadne Bosman[a], Natasha Appelman-Dijkstra[b], Joop van den Bergh[c], Arend Bökenkamp[d], Annemieke Boot[e], Martin de Borst[f], Bram van der Eerden[a], M. Carola Zillikens[a]

[a]*Erasmus MC- University Medical Center Rotterdam, Department of Internal Medicine, Rotterdam, Netherlands*

[b]*Leiden University Medical Center, Department of Internal Medicine, Leiden, Netherlands*

[c]*VieCuri Medical Center, Department of Internal Medicine, Venlo, Netherlands*

[d]*Emma Children's Hospital- Amsterdam University Medical Center- Vrije Universiteit, Department of Pediatric Nephrology, Amsterdam, Netherlands*

[e]*University Medical Center Groningen, Department of Pediatrics, Groningen, Netherlands*

[f]*University Medical Center Groningen, Department of Internal Medicine, Groningen, Netherlands*

Background/Introduction: Phosphate is critical for skeletal development and mineral metabolism. Phosphate deficiency leads to e.g. muscle weakness and rickets or osteomalacia. Several inherited and acquired causes of renal phosphate wasting can lead to hypophosphatemic rickets (HR). X-linked hypophosphatemia (XLH) is the most common form of HR with an estimated prevalence of 1:20.000. The prevalence of chronic hypophosphatemia in the Netherlands and the clinical manifestations are currently unknown.

Purpose: ORPHOS-NED has been developed to identify and evaluate patients with XLH and other forms of chronic hypophosphatemia within a registry in the Netherlands.

Methods: ORPHOS-NED is a web-based registry that has been set up by a group of medical specialists, who are affiliated to the Dutch Federation of Nephrology (NFN) and the Bone Network of the Dutch Society of Endocrinology (NVE). Dutch endocrinologist and nephrologists are approached for eligible patients. Children and adults with chronic hypophosphatemia are considered for inclusion. After informed consent, a chart review is performed to collect data on several aspects of the disease: initial presentation; symptoms; radiological, genetic and laboratory examinations; treatment; and follow up. Furthermore, questionnaires are sent out to assess health-related quality of life including the Brief Fatigue Inventory, the Brief Pain Inventory, RAND36, the Health Assessment Questionnaire and the Pediatric Outcomes Data Collection Instrument.

Results: Currently, 83 pediatric and adult patients from 3 academic hospitals have been included in this registry. Inclusion of patients is ongoing. The data from this registry will lead to more insight in the prevalence, natural history, treatment and its effects on HR, quality of life, and into genotype-phenotype relations in the different genetic forms.

Conclusion(s): A Dutch nationwide registry is being set up for genetic and acquired forms of chronic hypophosphatemia, which will lead to improved insight in prevalence, causes, disease manifestations and therapy.

doi:10.1016/j.bonr.2021.101003

P195

Activin-A induces differential gene expression exclusively in periodontal ligament fibroblasts from fibrodysplasia ossificans progressiva patients

Ton Schoenmaker[a], Michal Mokry[b], Dimitra Micha[c], Coen Netelenbos[d], Nathalie Bravenboer[e], Marjolein Gilijamse[f], Marelise Eekhoff[d], Teun de Vries[a]

[a]*ACTA, Department of Periodontology, Amsterdam, Netherlands*

[b]*UMC Utrecht, Division Laboratory- pharmacy and biomedical genetics, Utrecht, Netherlands*

[c]*Amsterdam UMC, Department of Clinical Genetics, Amsterdam, Netherlands*

[d]*Amsterdam UMC, Department of Internal Medicine section Endocrinology, Amsterdam, Netherlands*

[e]*Amsterdam UMC, Department of Clinical Chemistry, Amsterdam, Netherlands*

[f]*Amsterdam UMC, 6Department of Oral and Maxillofacial Surgery and Oral Pathology, Amsterdam, Netherlands*

Background/Introduction: Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disease characterized by heterotopic ossification (HO). It is caused by mutations in the Activin receptor type 1 (*ACVR1*) gene resulting in enhanced responsiveness to ligands, specifically to Activin-A. Though it has been shown that capturing Activin-A protects against heterotopic ossification in animal models, the underlying mechanisms at the gene expression level causing ossifications and progression are unknown.

Purpose: Unraveling the mechanisms by which Activin-A mediates heterotopic ossification in FOP has become increasingly relevant given the promising, disease-limiting results in FOP patients in the first clinical trial with Activin-A antibodies. We investigated the transcriptomic changes induced by Activin-A of healthy control and patient-derived periodontal ligament fibroblasts (PLF) isolated from extracted teeth by RNA sequencing analysis.

Methods: To study early differences in response to Activin-A, periodontal ligament fibroblasts from 6 control teeth and from 6 FOP patient teeth were cultured for 24 hours without and with 50 ng/ml Activin-A and analyzed with RNA sequencing.

Results: Pathway analysis on genes upregulated by Activin-A in the FOP cells showed an association with pathways involved in Activin, TGFβ and BMP signaling. Gene ontology (GO) analysis using a Benjamini and Hochberg's False Discovery Rate of 5% showed an association, only in FOP cells, with GO terms that can be linked to cell adhesion, cell binding to substrate, and response to endogenous stimulus. When applying more stringent statistical criteria, differential gene expression induced by Activin-A was exclusively seen in the FOP cells. The upregulated genes with fold changes higher than 2 after 10% False Discovery Rate correction, like *SHOC2*, *TTC1*, *PAPSS2*, *DOCK7* and *LOX* are all associated with bone metabolism.

Conclusion(s): Our open ended approach to investigate the early effect of Activin-A on gene expression in control and FOP PLF shows