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Abstracts

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cranial imaging at 6-9 months of life in achondroplasia, whereas American Academy of Pediatrics recommends to evaluate every infant with achondroplasia for cranio-cervical junction risks via neurologic examination, polysomnography and neuroimaging either with computerized tomography (CT) or magnetic resonance imaging (MRI) as soon as the diagnosis is recognised. Here we present an infant with achondroplasia and FMS who presented with syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to significant FMS and myelocompression. Our aim is to draw attention to the early presentation of a life-threatening complication of achondroplasia and to discuss the optimal timing of cranial MRI.

Case Report: A 2-month-old boy with prenatally diagnosed achondroplasia was referred to our university hospital due to disordered breathing and altered consciousness. On physical examination, the patient was apathic, pale, hypotonic and hypothermic (34.8°C) and had typical features of achondroplasia. Shallow breathing with nasal flaring and suprasternal retractions and deep sighing was compatible with central apnoea, blood gas analysis revealed respiratory acidosis. The patient was intubated in our paediatric intensive care unit. Laboratory investigations revealed severe hyponatremia (114 mmol/l) and hypochloridaemia (82 mmol/l) with normal glucose and urea levels and high urinary sodium-output (131.8 mol/mol Cr). The diagnosis of SIADH was made based on low serum osmolality (237 mOsm/kg) in the presence of high urine osmolality (431 mOsm/kg) and treatment was started. An emergency CT showed a high-grade stenosis at the cranio-cervical junction, subsequent MRI demonstrated myelocompression (AFMS 4b). The patient underwent decompression surgery the next day. A prompt improvement of laboratory parameters was observed after operation with an increase in serum osmolality (290 mOsm/kg) and a decrease in urinary sodium extraction (42 mol/mol Cr). Spontaneous breathing after extubation was sufficient but only reduced spontaneous motor activity of the extremities was observed in the course, hence a high-level spinal injury can be assumed.

Conclusion: Clinicians should be aware of SIADH as a presenting sign of FMS in children with achondroplasia. Further discussion is needed regarding improved family education and timing of screening recommendations including neuroimaging especially in children who did not receive polysomnography.

P1-25

Efficacy and safety of bisphosphonate treatment in pediatric patients with osteoporosis caused by immobilization

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Introduction: Osteoporosis is medical condition commonly associated with immobilization in children, which can lead to a vicious cycle of disability, worsening osteoporosis, and recurrent fractures. Currently, bisphosphonates are widely used as a standard therapy in children with osteoporosis, but there are limited data on efficacy according to its dosage and duration. We aimed to evaluate efficacy of bisphosphonate treatment according to the dosage and duration in pediatric patients with osteoporosis due to immobilization.

Method: We reviewed medical records of pediatric patients who were diagnosed with osteoporosis due to immobilization rated as Gross Motor Function Classification System (GMFCS) grade V, and who received bisphosphonate therapy with regular check-up for at least 1 year. The dosage and duration of the treatment, biochemical laboratory measurements, data of bone densitometry, and the occurrence of side effects were collected.

Results: Subjects were 21 children. The average duration of bisphosphonate treatment was 2.0 ± 0.9 years, and mean cumulative dose per body weight of bisphosphonate was 7.7 ± 2.5 (mg/kg/year). After the treatment, mean lumbar spine bone mineral contents (BMC) significantly increased from 14.20 ± 8.58 (g) to 19.38 ± 9.89 (g) ($p<0.05$), lumbar spine bone mineral density (BMD) significantly increased from 0.40 ± 0.14 (g/cm2) to 0.49 ± 0.14 (g/cm2) ($p<0.05$), and height-adjusted lumbar spine BMD Z-score also showed improvement from -2.66 ± 1.66 to -1.66 ± 1.38 with statistical significance ($p<0.05$). The cumulative dose and the duration of treatment were not related to its efficacy, but increasing average dose per body weight in each cycle (mg/kg/cycle) showed significant effects on increasing change in height-adjusted lumbar spine BMD z-score (regression coefficient $\beta = 1.065$, $p < 0.05$).

Discussion: BMC, BMD, and height-adjusted BMD z-score significantly increased after bisphosphonate treatment in pediatric patient with osteoporosis due to immobilization. Independent of cumulative dosage and duration, the efficacy of bisphosphonate treatment increased significantly as average dose per body weight in each cycle increased. Further studies with sufficient number of subjects and long term follow-up observation are needed.

P1-26

Outcomes of four patients with osteonecrosis after one-year pamidronate treatment

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Background: Osteonecrosis (ON) is bone death caused by inadequate blood supply resulting in demineralization and trabecular thinning and, subsequently, mechanical failure. Although the pathophysiology of ON is not fully understood, the use of high-dose glucocorticoid (GC) is one of the triggers. Furthermore, its optimal management remains uncertain. The use of

bisphosphonates (BP) for the treatment of ON has been reported, however, data on outcomes are limited.

Method: The patients who were evaluated in our unit regarding ON during the last two years were included. Data regarding clinical, laboratory, and imaging studies MRI, and bone mineral density measurements (BMD) were recorded before and one year after treatment (reevaluation). The severity of the clinical picture was assessed using Common Terminology Criteria for Adverse Events (CTCAE) criteria (between 1 (asymptomatic) and 5(death)). Patients were treated with pamidronate (1mg/kg/day, with a maximum dose of 60 mg/day, for two days, quarterly) and, when needed, calcium, vitamin D, and physiotherapy.

Results: There were four female patients (Patient 1, acute lymphoblastic leukemia treated with bone marrow transplantation; Patient 2, immune thrombocytopenic purpura, Patients 3 and 4, systemic lupus erythematosus) aged between 10 and 17 years. Only Patient 1 was prepubertal. According to CTCAE, ON was consistent with Grade 3 (Severe symptoms; limiting self-care activities of daily living; elective operative intervention indicated) and multifocal in lower limbs in all of them. Surgical core decompression in Patient 4, which had been performed before pamidronate, did result in clinical improvement. All of them had been treated with high-dose GC. None of them had any fractures. Calcium, phosphorus, alkaline phosphatase (ALP), vitamin D, and parathyroid hormone levels were normal in all patients before, during, and one year after pamidronate administration. The BMD SD scores were all normal for P1, P2, and P4. Patient 3 had a normal BMD SD score (1.2 SDS) before treatment, but it increased to 2.9 SD score at reevaluation. No other side effects related to the use of bisphosphonates were observed. At the time of reevaluation, the lesions were stable on MRI and their clinical condition was consistent with Grade 1 according to CTCAE (Asymptomatic; clinical or diagnostic observations only; intervention not indicated).

Conclusion: Pamidronate may be an effective treatment for the improvement of symptoms related to ON.

P1-27

Effects of pharmacological inhibition of BCL-2 on linear bone growth

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Introduction: The survival rates for childhood cancer have significantly increased over the past decades but the management of treatment-related complications remains challenging. Thus, the introduction of novel drugs requires careful investigation of potential off-target side effects. The developing skeleton is severely affected by the anticancer treatment which may result in growth retardation and short stature. Venetoclax is a selective Bcl-2 inhibitor which is under investigation in pediatric cancer clinical trials. However, there are no data regarding the potential side-effects of venetoclax on the bone tissue.

Objectives: The overall aim was to investigate the effects of venetoclax on bone growth. Mitochondrial activity and the Bcl-2 pathway are crucial during bone development, we hypothesized that venetoclax might suppress bone growth by inhibiting Bcl-2 in the growth plate.

Methods: (a) Culture of ATDC5 cells: The chondrogenic ATDC5 cells were cultured with venetoclax (0.625-2.5 μM) or DMSO and cell viability was assessed after 48 or 72 hrs with the CellTiter-Glo® Luminescent Cell Viability Assay. (b) Culture of fetal rat metatarsals: E20 rat metatarsals were cultured ex vivo with venetoclax (1 nM-10 μM) for 12 days (n=15). Photos and length measurements were taken at designated time-points to monitor growth and histomorphometric analysis was performed. (c) In vivo studies: Female NMRI nu/nu mice (7-week-old, n=4-5) were treated with venetoclax (100 or 200 mg/kg via oral gavage) or vehicle for 14 days. X-rays were taken to evaluate longitudinal bone growth and changes in the growth plate were assessed with histomorphometry.

Results: Venetoclax decreased cell viability in ATDC5 cells after 48 or 72 hrs culture. Venetoclax-treated metatarsals showed decreased growth from day 0 to day 12 compared to the control group (2.5 μM: 65.4 ± 3.4 % vs control 76.4 ± 1.5%, $p<0.05$; 5 μM: 20.2 ± 1.4 % and 10 μM: 9.5 ± 1.1% vs control 76.4 ± 1.5%, $p<0.001$). Furthermore, the height of resting + proliferative zone and the size of hypertrophic cells were significantly reduced in the venetoclax groups. Venetoclax in the highest dose significantly reduced tibia growth in vivo ($p<0.05$) and both doses reduced growth plate height compared to vehicle (100 mg/kg: 130.2 ± 3.3 μm, $p< 0.01$; 200 mg/kg: 130.6 ± 4.9 μm, $p< 0.05$ vs vehicle: 151.4 ± 4.9 μm).

Conclusion: Our findings show that venetoclax impairs chondrogenesis and induces growth retardation. Based on these, further investigations will enable the identification of the mechanisms involved in the observed side-effects on bone.

P1-28

Pain as an onset symptom in hereditary hypophosphatemic rickets with hypercalciuria, a case report

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We report a case of hereditary hypophosphatemic rickets with hypercalciuria (Hereditary Hypophosphatemic Rickets with Hypercalciuria, HHRH) in a 13-year-old boy, referred for evaluation due to the onset of bilateral knee pain for about two years. Pain was intermittent and walking limiting and negatively affected quality of life. Negative family history of bone/joint pathologies and kidney stones. The parents are consanguineous (first cousins), have normal stature and no history of bone and mineral disorders.

Physical examination revealed normal height and weight. There were no skeletal deformities.

Hypophosphatemia was found on blood tests (2.7 mg/dL, normal for age 3.30-5.70) associated with high urinary excretion of phosphates (reduced TRP) and high urinary excretion of calcium (6.1 mg/ kg/day, normal <4 mg/kg /day). There were also elevated 1,25-vitamin D values (141 pg/mL, normal value 42-95 pg/mL)