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Proceedings of the Second Middle East Metabolic Bone Course; 10-11th March 2017, Dubai, UAE

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Abstract

The second Metabolic Bone Disorders Course was organized by the Arab Society for Paediatric Endocrinology & Diabetes (ASPED) and the European Society for Paediatric Endocrinology (ESPE) in collaboration with the UAE University. The first day of the course had scientific and educational sessions on the metabolic bone disorders of Rickets, Osteogenesis Imperfecta (OI) and Hypophosphatasia (HPP) and included presentations of the subjects and cases by regional and international experts, who had been selected by the Scientific Committee. The second day had various sessions on disorders of calcium metabolism detailing various causes and case scenarios on hypocalcemia and hypercalcemia. A session was allocated for multidisciplinary health care professionals involved in metabolic disease which included talks by a Paediatric Rheumatologist, Orthopaedic surgeon and clinical biochemist. The final session on day 2 centred around skeletal dysplasia and various forms of miscellaneous bone disease. A summary of systemic manifestation of bone disease and role of paediatric endocrinologist in metabolic disease was highlighted. The speakers shared their expertise and regional experiences in the management of these disorders. Each topic was followed by a discussion session where the health care practitioners highlighted the challenges, regional and otherwise, in the management of these disorders. Ways to appropriately manage these disorders more efficiently was discussed with global standards.

Keywords: Rickets; Hypocalcemia; Hypercalcemia; Hypophosphatasia

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Summary of Proceedings

Day 1

The first day of the meeting focused on Rickets, Osteogenesis Imperfecta (OI) and Hypophosphatasia (HPP) and was conducted in 4 sessions which reviewed several facets of diagnosis and management of these conditions.

Session I: Rickets

Chairpersons: Dr Abdelhadi Habeb and Dr Jaishen Rajah

The Spectrum of Phosphate Disorders with Special Emphasis on X Linked Hypophosphatemic Rickets (Xlhr) – Dr Nick Shaw

Prof Nick Shaw focused his presentation on the x-linked hypophosphatemic rickets (XLHR), caused due to mutations in the *PHEX* gene as the most prevalent genetic form of XLHR. He discussed the key mechanisms in bone formation involving phosphate synthesis and the role of the fibroblast growth factor 23 (FGF23). The synthesis of FGF23 is inhibited by low phosphate levels. The most important diagnostic tools in the assessment of XLHR were discussed, including the levels of phosphate and creatinine both in the urine and plasma as well as the comparative values between these. He noted that TmPO4, the renal re-absorption threshold of phosphate, is a more accurate indicator of XLHR than plasma phosphate level, which is influenced by the therapeutic doses of phosphate

administered. Other diagnostic modalities like radiological investigations were discussed. The treatment objectives were reviewed and he advised close monitoring of the plasma calcium levels to balance the plasma creatinine. The presentation highlighted the relevance of early diagnosis and treatment as this has a direct impact on the bone growth and height which should be attained in the early ages. The therapeutic effects of anti-FGF23 antibodies in the treatment of XLHR were discussed. The interim results of the Phase-3 study to assess the efficacy and safety of KRN23 in adults with x-linked hypophosphatemia (XLH) was also reviewed. The other forms of hypophosphatemic rickets like ADHR and ARHR were briefly reviewed including s the *ENPP1* mutations and the diagnostic differences in biochemistry values between them. Dr Shaw highlighted the major diagnostic difference in ENPP1 namely, the normal urine calcium level and the early onset hearing loss. Manifestations of FGF23-related hypophosphatemia like epidermal nevus syndrome were also discussed. Other causes of hypophosphatemia, such as the non-FGF23-mediated hypophosphatemic rickets with hypercalciuria and Dents disease were reviewed with focus on their relevance to the differential diagnosis of XLHR. Dr Shaw stated that he anticipated better prospects for the management of XLHR with the anti-FGF23 antibody.

XLH rickets: A case scenario – Dr Badi Alenazi

Dr Alenazi discussed a case from KSA, of an 18-month-old boy, who presented with a history of bowing of the legs since he turned 12 months, with no other noticeable bone deformities. He was initially diagnosed at a local hospital with nutritional rickets and started on vitamin D3 and cholecalciferol. After 4 months of good compliance to the medication without any response, he was referred to a tertiary centre. The child had 6 siblings and there was no history of bone disease or rickets in the family. The investigations revealed low plasma phosphate and tubular re-absorption of phosphate. X-rays showed active rickets. XLHR was suspected and the patient was referred for genetic testing, which revealed PHEX mutation. The patient was treated with 1-alpha hydrocalciferol and oral phosphate, and was followed up in the out-patient clinic. His bone profile showed significant improvement, however, the bowing of legs persisted even at 3½ years and so corrective osteotomy was scheduled.

Vitamin D deficient rickets, not always nutritional – Dr Angham Mutair

Dr Mutair discussed the case of a child with short stature who presented at the age of 10 years. She had normal development and good nutrition, but significant juvenile bone pains and some limitation of physical activity. She had slight bowing of lower limbs, but no other obvious rickets symptoms. In the peripheral clinic, she was treated with vitamin D3 without significant improvement. She has one brother with significant skeletal deformities including bowing, which was surgically corrected at a tertiary hospital. She discussed the x-ray of both siblings which manifested a vitamin-D deficient rickets skeletal pattern. The biochemical profile showed slightly high PTH and low vitamin D. The patient was started on Calcium and vitamin D3 without improvement. Endoscopy was done for malabsorption studies which turned out normal. Genetic studies revealed heterozygous *CYP2RI* mutation. She stated that homozygous mutations express more clinically than heterozygous mutations. She presented a few studies conducted in the region involving families with strong history of bone deformities. She concluded the presentation with a recommendation for CYP2RI analysis for patients presenting with symptoms of vitamin-D deficiency even with good nutrition and family history of bone deformities, who fail to respond to low doses of vitamin D. The suggested therapy was high dose of vitamin D, 50,000 IU and noted that so far only 4 mutations have been identified for 25-hydroxylase vitamin D deficiency and the *CYP2RI* gene is a major player in the synthesis of 25-hydroxy vitamin D. She emphasized the importance of screening *CYP2R1* in children, and stated that this mutation should be suspected if a patient presents with vitamin D deficiency that does not respond to supplementation.

Hereditary rickets, case scenarios – Dr Mohammad Aldubayee

Dr Al Dubayee presented the case of a 17-month-old girl child born out of a consanguineous marriage. She was late to walk and had significantly delayed dentition. Family sought medical advice at the age of 9 months and she was started on vitamin D and calcium supplements. She then presented with classic signs of rickets. The biochemical profile showed high PTH, very high ALP, significantly low 1, 25 Dihydrocholecalciferol (1, 25 DHCC) and low calcium. The 25 hydroxy vitamin D was, however normal. Genetic testing revealed both parents to be carriers of VDDR Type I. The patient was started on Alfacalcidol and showed a good progress with normalization of ALP and 1,25 DHCC. However, kidney function remained a concern. The skeletal improvement was discussed with pre- and post-therapy x-rays. The diagnosis was VDDR Type IA with *CYP27B1* genetic mutation. The speaker stated that the VDDR IA responds well to Alfacalcidol therapy and even though the treatment must continue lifelong, the doses can be reduced in the long run as the disease becomes more manageable. He stated that this case illustrates that the scope of investigations have to be widened in some cases to ensure proper diagnosis and management.

Summary of Discussions

The audience shared their experience with hereditary forms of rickets in the KSA and noted that in addition to HPPR and VDDR Type 1, they see a large number of VDDR Type 2 cases making it the largest pool of VDDR Type 2 case in the region. It was highlighted that most of these patients have repeated admissions for IV Calcium as they reach puberty as they become unresponsive to vitamin D therapy. This status of resistance seems to become less pronounced as patients pass the puberty stage when they become less resistant to vitamin D and will start responding to high doses of oral vitamin D. It was commented that osteotomy at 3½ years, as in the HPPR case presented by Dr Alenazi, may be too early as there are still plenty of opportunities and time for correction via conservative methods, including phosphate and Alfacalcidol therapy. It is advised that osteotomy to be postponed until the growth phase is completed. In addition, it was highlighted that osteotomy is a big operation

and requires up to 6 months of stabilisation. It was suggested that epiphysiodesis can be an alternative as it is a much simpler procedure. Epiphysiodesis is done around the growth plates to adjust the angle of the knees and ankles. In reference to the HPPR with hypercalciuria case presented by Prof Shaw, it was highlighted that it is probably more common in this region and that it can present with hypercalciuria and renal stones without any apparent bone deformities. The importance of monitoring for hypercalciuria before and after treatment was pointed out. The impact of phosphate levels on PTH and 1, 25 DHCC and requirement of calcium supplementation in cases of HPPR presenting with normal/high PTH and low calcium were discussed. It was mentioned that calcium supplementation is not required because the plasma calcium will be normal and that calcium supplementation can increase the risk of nephrocalcinosis and renal stone formation. The site of deformity and the prevalence of varus exaggeration in most of the HPPR cases was reviewed. It was stated that the site of deformity depends on physiological preference related to age and has no correlation with variety of rickets. In the early stages of life, i.e. up to 3 years, the physiological preference is for varus position and becomes valgus after the age of 3 years. He concluded that if the disease impacts in the early ages, it presents as varus deformity. Geneticists in the audience commented that whole genome sequencing should be considered if no improvement on treatment is observed. This is due to the fact that skeletal dysplasia is common in the region and might be underdiagnosed on clinical grounds. However, it was pointed out that since improvement in bone deformities only becomes evident after a year or two of initiation of treatment. Adequate duration of treatment should be allowed before considering a change in management. The late age of presentation of these cases and the mean age at presentation of 6 years was discussed. It was described that in a typical scenario, the patients are usually assessed and treated by several other specialists before they are presented to the paediatric endocrinologist specializing in metabolic bone disorders. This leads to late diagnosis and late initiation of appropriate therapy in most of the cases. The importance of performing appropriate baseline investigations in all cases presenting as rickets was emphasized. Storing serum for later investigations can be useful as initiation of a treatment alters the biochemical profile and can complicate the differential diagnosis. The correlation of 25 OH D levels to the clinical manifestation of rickets was addressed. It was noted that not all patients with low 25 OH D levels manifest the disease. It was pointed out that this could be due to minor genetic variations of heterozygous mutations which might manifest a mild form of the disease. Furthermore, absence of any disease in the event of low 25 OH D could be due to a semi-autosomal dominant gene. The clinical manifestations in such patients may be dependent on dietary intake of calcium. Low calcium intake may cause a higher chance of manifestation of the disease and can be treated by supplementing calcium either orally or intravenously. The reference range of 25 OH D and the variation in the normal range with age was discussed. It was stated that assays for measuring 25 OH D have different reference ranges and the range does not need to be adjusted for age. It was commented that *PHEX* mutation can be identified in 70-80% of XLHR patients with the rest not being identified. It was agreed that if the clinical and biochemical picture is clear, there should be no need to wait for genetic confirmation to start the treatment. On the HPP discussion, the main recommendations centred around the importance of standardizing the range to ALP to age specific limits and the necessity of alerting to low ALP level by biochemistry labs.

Highlights

1. Osteotomy corrections of bone deformities should wait until the growth phase is completed and the patient reaches puberty. Epiphysiodesis may be a better option for correction at younger age.
2. Monitor for hypercalciuria before and after treating HPPR.
3. Calcium supplementation is not required in HPPR with high PTH and low calcium.
4. Give adequate time for the therapy to take effect on bone deformities before thinking of changing management.

Session II- Osteogenesis Imperfecta

Chairpersons: Dr Mohamed Abdul Jabbar and Dr Mona Al Khawari

Osteogenesis Imperfecta: An overview – Dr Zulf Mughal

Prof Zulf Mughal discussed OI, a heterogeneous group of connective tissue disorders associated with increased fragility and propensity to bruising with or without trauma. It is characterized by low bone mass leading to deformities affecting the skull base, rib cage, spine and limbs, and is a high bone turnover disease in children. The other clinical features were discussed in brief including dental and muscular disorders, and bone and muscle fragility. Prof Mughal mentioned that blue sclera is a hallmark of most, but not all patients with OI. The structure of bone and type-1 collagen was presented in detail to discuss the possible primary defects in collagen formation leading to bone deformities in OI. The Sillence Classification of OI was presented and discussed in detail. The clinical manifestations including general fragility of tissues including skin, hyper-extensibility of the joints, propensity to hernia and deafness, wormian bones and the blue sclera were discussed and the scales for grading the blueness were reviewed. The Beighton classification of joint hypermobility was presented and some of the factors which affect the QoL of the patient were discussed. The relevance of podiatric support and proper footwear to distribute the load evenly in OI patients was explained. Myopathy, another factor which affects the QoL and the ability to write, and its implications were discussed. Prof Mughal pointed out that dental manifestations including fragile dentine structure may necessitate close follow-up with dentists. The Ole Worm classification and the rate of occurrence of wormian bones in children with OI was discussed and concerns with skull base fractures were reviewed. Prof Mughal discussed vertebral compression fractures, and stated that they were very common in OI due to skeletal fragility and usually occur without trauma. He pointed out that all cases in his practice are assessed with DEXA Scan to detect insidious fractures which occur frequently in these children. Prof Mughal discussed the case of a

7-year-old boy to illustrate the risk of misdiagnosis and highlight the importance of early diagnosis. The patient in discussion had intrauterine rib fractures and inguinal hernia at birth, both of which were treated immediately at birth with bisphosphonate to help heal fractures and prevent spine deformities. The diagnosis of OI type IV, was made in-utero, and eventually the patient had a straight spine, is capable of walking and generally faring well. He then described the case of OI Type V *COL1* and noted that these patients have very thin ribs and have very characteristic metaphyseal bands. He discussed about the IFITM5 mutations, which are autosomal dominant mutations, without blue sclera or dentinogenesis and propensity for development of hyperplastic calluses, which may be the most salient feature. He stated that, as they grow older these patients develop calcification of the intraosseous membrane, which are usually confused with osteosarcoma. He suggested giving these patients indomethacin to reduce the callus formation. He discussed OI Type VI, which is a recessive form in which patients develop compression fractures. He pointed out that bone biopsy will reveal mineralization defect in such patients, who may also have osteomalacia and classic fish scale pattern under polarized light. The mutation is homozygous in the SERPINF1 gene. He noted that even in Europe, there is no standardization of therapy, and said that in Germany the preference is to treat with denosumab as bisphosphonate is not considered to be effective, while in UK bisphosphonate is preferred. He discussed the case of a patient who fared well under treatment and was brought to him by lawyers as she was removed from parents suspecting abuse due to recurrent fractures. An underlying disease was suspected when she had bruises in foster care as well. He stated that the patient is now 18 years old and studying law in UK, albeit wheelchair bound. The other forms of recessive OI such as the *CRTAP, LEPRE1* and *P3H1* mutations were also discussed and presented. A case of CRTAP with Cole-Carpenter syndrome was also presented. Prof Mughal emphasized the importance of multidisciplinary care along with medical treatment and stated that physiotherapists play a crucial role in ensuring good QoL along with podiatrists and liaison with school therapists. Bisphosphonate therapy was further discussed including the action of the drug after being taken up by the osteoclasts, the effects of the IV drug on bone formation as well as the side-effects including acute phase reaction on initial introduction to the drug. The relevance of optimization of vitamin D level before starting bisphosphonate therapy, to avoid hypercalcemia, especially with zoledronic acid was emphasized. The importance of continuing bisphosphonate therapy without interruptions until bone growth is completed was highlighted by demonstrating the case of 'interface stress zebra lines' on x-ray where therapy was interrupted and was evident as treated and untreated zones. Prof Mughal concluded the presentation with a case of OI Type III, born with multiple fractures, who was treated with bisphosphonate and multidisciplinary management resulting in improved the bone structure, restitution of integrity of the spine and ability to walk with support. The case was shown to illustrate the positive impact of bisphosphonate therapy and multidisciplinary support on OI.

Osteogenesis Imperfecta: Experience from Kuwait – Dr Ayed Al Anezi

Dr Al Anezi described the gamut of healthcare facilities and services in Kuwait and said that all multidisciplinary facilities, including a dedicated genetic center and a center for pre-implantation genetic counseling, were available in Kuwait currently. However, he noted that patients generally find access difficult owing to the far-way locations of these facilities. The common referral scenarios of OI patients were presented, stating that they are usually referred as severe rickets cases and sometimes are referred due to family history of bone deformities and when a baby is born with blue sclera. He said that it is not possible to accurately estimate the prevalence of the disease in Kuwait as registry for rare diseases does not exist. He pointed out that available data is from retrospective studies of cases from several hospitals in the country. He presented a case of a father and his eldest son, both of whom had blue sclera. The father was of normal height and hearing and was working as a policeman without any major issues. He had a history of childhood fractures at 7 and 11 years of age. The son had repeated fractures since the age of 6 months, at 4 years he had a fracture of the femur. He received pamidronate for one year and the fractures stopped for a while. At the age of 8 years, he started to have repeated fractures with mild trauma. The patient was referred to a tertiary center after the orthopedic surgeon noticed extremely brittle bones. The family was requested to bring all affected children and the mother brought the 4 children who all had blue sclera and history of childhood fractures. Dr Al Anezi pointed out that the mother could distinguish the affected children by the color of their sclera. DEXA scans and the bone mineral densities pertaining of the patients were discussed. The speaker pointed out that Z-score should be used for osteoporosis and osteopenia as it is more suitable for growing children. Dr Al Anezi mentioned data interpretation as one of the biggest challenges in assessing bone mineral density as there is no standardized and physiologically adjusted normative data available for reference. The normative data in Kuwait currently has only age and gender parameters covering ages 4-12. He noted that physiologic maturity parameters like height and weight are highly variable during the pubertal growth spurt and the bone mineral density also increases to peak during the pre-pubertal stage. He highlighted the importance of adjusting the normative data with these physiological parameters. Other parameters he recommended were Tanner stage, weight, and ethnicity. He stated that bisphosphonates are the preferred drug for OI in Kuwait and that endocrinologists have a good experience with pamidronate and zoledronic acid. He added that he follows the Royal Manchester Children's Hospital guidelines and prefers to use Pamidronate. The therapeutic regimen was discussed in detail. He noted that currently, Zoledronic acid is also widely used in the treatment and the corresponding regimen followed in Kuwait was discussed. He concluded the presentation highlighting the future challenges including, establishing a registry for OI in Kuwait, increasing the awareness about OI among other specialties, especially orthopedics to expedite the referral and bring down the referral age, building up a dedicated center for management and research of the disease, provide more active

PGD service for the families with OI history, physiotherapy and rehabilitation facilities and need for OI Support group.

Osteogenesis Imperfecta: Experience from Egypt –Prof Rasha Tarif

Prof Tarif started the presentation with a review of the history of OI. She discussed the pathophysiological aspects of the disease and then the Sillence Classification of OI and the autosomal recessive and dominant varieties of the disease as well as other associated syndromes. This was followed by a detailed discussion of the differential diagnosis of OI. She stated that it is often possible to diagnose OI based solely on the clinical pictures and radiological evidence and added that the features of the same type of OI can vary widely between individual cases, even within the same family and same type of OI. She opined that all clinical or radiological features do not fit into the predefined criteria for diagnosis. She mentioned that even though genetic testing is a reliable indicator, it is not done routinely in Egypt as it is expensive and not easily accessible. She cautioned that though x-ray studies and the blue sclera are clinical indicators they may not be adequate to establish the diagnosis of OI. A suspicion of abuse, owing to easy bruising, in patients with OI often delays the diagnosis. Prof Tarif presented some cases from her clinical practice which illustrated the diagnostic difficulties, therapy and psychological impact of the disease on the patients. Three of the cases she presented had normal sclera, highlighting the fact that this cannot be used as the pathognomonic indicator for OI diagnosis. The x-rays and clinical features of these patients were discussed in detail. The first case had flaring metaphyses, typical popcorn appearance and callus formation. A type 1, milder form was discussed where the patient presented with blue sclera, short stature, mild osteopenia, and history of fracture. The patient was treated with zoledronic acid and showed significant improvement. She presented a case of a father and 2 sons with OI type IV, the elder one with history of recurrent fractures, the younger one with no history of fractures. The other features were common including the normal sclera and hearing. She also presented the case of an OI type V patient who presented with normal sclera, thin ribs, decreasing hearing, dentinogenesis imperfecta, codfish vertebrae and a history of recurrent fractures and severe osteopenia. She presented another case, which was initially diagnosed as type IV, but later confirmed as type V with the appearance of mineralization of the interosseous membrane in the later years, metaphyseal radio-dense bands, and hypertrophic callus formation in the femur. This patient was reported to have a rare mutation in *IFITM5* after referral to a genetic center. Prof Tarif highlighted the need for genetic testing facilities and the challenges faced in their absence. She presented another 2 cases who were misdiagnosed initially. The case of an OI type 8, genetically confirmed as *LEPRE1*, but initially thought of as OI type 4 was presented. She discussed another case report where the patient was diagnosed as OI type 4, but symptoms were not relieved with pamidronate. She added that radiological evidence revealed OI Type 6 and was confirmed to have a *SERINF1* gene mutation by genetic screening done in Turkey. Prof Tarif shared the Ain Shams University protocol and checklist for OI management and follow-up. She highlighted the relevance of a multidisciplinary team in the management of OI, which also includes a paediatric psychologist, and follow-up with yearly DEXA Scans. She mentioned that reference ranges for DEXA scans in pediatric age group is not yet available and added that oral calcium is given according to recommended daily intake (RDI) and age along with prophylactic vitamin D supplementation. She noted that the challenge is reducing the fracture incidence and severity and considers bisphosphonate as the corner stone of management. She stated that though both pamidronate and zoledronic acid were used with same frequency earlier, lately zoledronic acid is preferred more in Egypt. She discussed the action of bisphosphonate in reducing bone loss and increasing the bone density. The protocol for zoledronic acid therapy was shared with the group. She mentioned the importance of monitoring serum creatinine levels to assess the kidney function and recommended interrupting the treatment until the serum creatinine reverts to normal to avoid renal failure. She presented the data from studies done at Ain Shams University, one comparing outcomes among patients with OI on zoledronic therapy and another assessing GH therapy in patients who are already on zoledronic acid therapy. She reported that there was no evidence of a significant impact of GH treatment on the growth velocity or the bone mineral density from the data. She stated that the effect observed may be solely the impact of zoledronic acid. She mentioned that OI imposes a heavy burden on families and the health system, and it is common in Egypt owing to consanguinity. The clinical and radiological signs overlap between the various types of OI. New mutant variations are emerging and genetic testing is not part of routine workup, but it will be good to diagnose new mutations. Addition of GH to treatment has no impact for OI patients. Bisphosphonates reduce the fractures and increase the growth velocity. She highlighted the importance of a multidisciplinary team in the management of OI cases and to ensure better QoL.

Summary of Discussions

Doctors from the KSA mentioned that in the year 2000, they started using bisphosphonates and since then around 50 patients were treated. In 2004, a group from the KSA published the radiological features of pamidronate treatment manifesting as zebra lines, that are widely arranged in the long bones with a rapid growth rate. The space between these lines corresponded to the frequency of therapy. These zebra lines are not strong lines and are prone to fractures. It was commented that these zebra lines are mineralized cartilages and they act as stress inter-phases within the bones. Sharing an experience from KSA, a paper published involving 131 patients on zoledronic acid over 12 years was discussed. Safety and efficacy of the drug was highlighted as concluded in the study. In the KSA, the drug is used across ages 6 months to 18 years and that it is preferred to pamidronate. It was highlighted that pamidronate is used until 2 years of age after which zoledronic acid is started in UK. However, in Australia, like KSA zoledronic acid is used right from birth. Age at starting therapy was addressed. When clinical features are apparent, good response on vertebral re-modelling is possible across all pediatric age groups. It was mentioned that some of the heterogeneous milder forms of OI manifests only later and

the first fracture without trauma can appear after teenage. On discussing side effects of bisphosphonate, it was mentioned that usual side effects are the acute phase reaction on initial introduction and the risk, though low, of interphase fractures. Recent data from Birmingham and Sheffield reported patients with a specific mutation around the C terminal end of the *COL1A* mutation, manifesting as high-bone mass OI. Bisphosphonate therapy in these patients may give rise to atypical fractures. Avascular necrosis of the jaw is another complication, which is seen in adults when started on higher doses of bisphosphonate. Audience were cautioned about this complication and advised on regular dental follow-up. Oral bisphosphonates have a rigorous protocol and hence are advised only in young adults as maintenance therapy. Several trials of oral bisphosphonate revealed a lower efficacy compared with IV formulation. Long term effects include some atypical fractures possibly through over suppression of normal bone remodeling. In Kuwait, pamidronate is not advised for more than 5 years in the adult. So, the use of other drugs like Denosumab was raised as it has lesser side effects compared with pamidronate. Desosumab, however, is documented to have a high risk of rebound hypercalcemia. Use of Denosumab for OI Type VI was preferred in Germany. In the UK, there is an ongoing trial evaluating the merits of replacing bisphosphonates with Denosumab. Other new drugs are coming up and they will have an impact on future therapeutic regimen. The magnitude and variability of response to bisphosphonate between the different recessive forms of OI was reviewed. In the KSA and Egypt, there is a higher incidence of recessive cohorts on which studies are currently ongoing. It was suggested that linking up genetics and response to treatment is required.

Highlights

1. The scope for misdiagnosis highlights the importance of accurate and early differential diagnosis.
2. Multidisciplinary care is important along with medical treatment for overall care of the patient.
3. Optimizing vitamin D level before starting on bisphosphonate therapy, especially with zoledronic acid, essential to avoid hypercalcemia.
4. It is important to increase awareness of OI among other specialists to expedite referrals and diagnosis.
5. Standardization of BMD reference parameters is necessary.
6. Genetic testing is not part of routine workup, but it will be useful to diagnose new mutations.
7. Addition of GH to treatment may not have a significant impact for OI patients.

Session III – Hypophosphatasia

Chairpersons: Dr Fatima Al Jasmi and Dr Hessa Al Kendari

An Overall Review on HPP – Dr Zulf Mughal

Prof Mughal presented an overview of HPP focusing on the pathophysiology of the disease, the clinical manifestations, diagnosis and associated challenges, and management. The initiation and the process of mineralization of the bone, cartilage and teeth were discussed. The role of the two main enzymes associated with the mineralization, *ENPP1* (associated with the synthesis of PPI) and *TNALP* (associated with breakdown of PPI to phosphate) were discussed. He stated that when ENPP1 and TNALP act in concert, the mineralization takes place in the right density at the right places. HPP is characterized by accumulation of PPI (inorganic pyrophosphate) which suppresses the hydroxyapatite crystal formation, a crucial step in the pathophysiology of bone mineralization. He explained that more than just a disorder of mineralization, HPP is an in-born error in metabolism caused by inactivating tissue mutation of TNALP, which leads to an increase in the levels of 3 metabolites - PPI, PLP (pyridoxal 5 phosphate, active form of vitamin B6) and ethanolamine. The measurement of these metabolites can help with the diagnosis and monitoring of HPP, he said. Deficiency of ALP leads to rickets-like phenotype particularly in younger infants. Its effects however go beyond the skeleton, and many of the children with HPP are profoundly myopathic, though the mechanism behind this is not fully understood. He briefly discussed the neurological impact of the disease such as epilepsy like seizures in severely affected children. He mentioned other rare neurological manifestations of HPP such as the acute demyelinating disorder seen in the Japanese population and stated that the skeletal consequences arise as a result of mineralization defect as well as the impact on musculature. He added that the hypoplastic ribcage of HPP leads to respiratory problems, particularly in infants and that most of the newborns require ventilator support and follow-up by intensivists. He also mentioned about the rheumatologic impact of HPP and noted that the failure to get calcium into the mineralization phase leads to defective bone formation, hypercalcemia, hypercalciuria, and nephrocalcinosis. The genetics of HPP and the inheritance patterns of some variants was discussed. The severe infantile forms of HPP are usually inherited as autosomal recessive genes. The milder juvenile forms are either dominantly or recessively inherited. The prevalence of HPP across the various ethnic and regional communities was discussed. He mentioned that there is no clear data available on the prevalence of mild and moderate varieties of HPP. Prof Mughal listed the 6 major clinical forms HPP, however the symptoms and manifestations overlap making the diagnosis very tricky and he discussed each of them in detail. Prof Mughal said that the perinatal HPP was the most lethal form of HPP and noted that the prognosis is poor for perinatal and infantile HPP. In perinatal HPP, one of the most severe types, there is demineralization of the skeleton in-utero and many children are still-born or die shortly after birth if they are not diagnosed and treated immediately. The classical clinical features of perinatal HPP were reviewed including the PLP dependent seizures. He presented a case of perinatal HPP, a baby born out of a consanguineous union, with narrow and thin ribs, profound craniomalacia, short rickety limbs, hypotonia who required aggressive ventilation since birth. He stated that perinatal and infantile HPP are among the known causes of hypercalcemia and that HPP patients have high PPI and the PTH is suppressed by the hypercalcemia. He emphasised that the hallmark of this condition is the very low ALP in relation to the age-adjusted reference

values for ALP and added that diagnosis of HPP in this case was made on the basis of low ALP and characteristic radiological features. The genetic analysis supported the diagnosis. He mentioned that the patient's biochemical profile, radiological profile as well as the clinical manifestations must be carefully considered to differentiate between OI, HPP, and rickets. He briefly spoke about the benign perinatal form of HPP, where the symptoms manifest in-utero, which usually either improve in-utero or shortly after birth, and he said that he is yet to see a case in his clinical practice. Prof Mughal stated that infantile HPP usually manifests within the age of 6 months and usually presents to general paediatrics as 'failure to thrive', from the effects of hypercalcemia and frequent urination. He noted that the general paediatricians should be aware of the presentation of HPP for appropriate referral. The patients have clinical features of rickets, hypotonia, cranial deformities, and may have PLP dependent seizures like perinatal HPP. He mentioned that infantile HPP is very rare and he has seen only one case in his practice. He mentioned that the diagnosis cannot be made with the radiological picture alone, and noted that it is the biochemical profile which confirms the diagnosis. He discussed about 'odonto-hypophosphatasia', the condition where primary dentition starts falling off along with root at very early ages. He presented a case, where the child, came with loss of primary dentition with root at the age of 20 months and walked with an in-toeing gait. The radiographs were unremarkable, without any signs of HPP and ALP was at the lower end of normal range. Results from the biochemical profile revealed very high PLP/PA ratio. He pointed out that plasma PLP values are influenced by nutrition and so red blood cell PLP, which is the accurate indicator of PLP value, should be measured along the ratio of PLP and Pyridoxic acid for an accurate profile. Prof Mughal reiterated the importance of clinicians looking at the whole picture including the patient's history, family history, clinical manifestations, complete biochemical profile, and radiological patterns to confirm the diagnosis. Prof Mughal explained that the juvenile HPP manifests as short stature, extremely weak children with chronic pain and fragility fractures in the childhood. The deposition of calcium phosphate crystals in the bone marrow can lead to BM oedema revealed by MRI. They usually present a picture of CRMO (chronic recurrent multifocal osteomyelitis) on radiology. He discussed a few cases of juvenile HPP presentation and reviewed the clinical manifestations, differential diagnosis and management. He again mentioned here the importance of "Age and Gender adjusted ALP Values" and reiterated the un-readability of the result if the reference value is "0". To highlight the relevance of looking at the whole picture, he presented the case of a white Caucasian child, born to unrelated parents, who presented with chronic pain and fragility fractures including femoral fracture without trauma who was initially treated with bisphosphonates. She presented to Prof Mughal at 13 years of age and was initially considered to be a case of Bruck syndrome. He pointed out that the ALP was at the lower end of normal range and could have led to wrong diagnosis. However, the PLP and pyridoxic acid ratio was checked, which was high and led to the accurate diagnosis. She was found to have a mutation in TNALP along with TGF beta-gene associated with Loeys–Dietz syndrome, a form of the Marfan syndrome. The diagnosis was confirmed as HPP after a complete bone metabolic profile including a transiliac bone biopsy. Prof Mughal noted that HPP is a rare disorder and the chances of missing the diagnosis are high if it is not promptly suspected when low ALP according to age and gender adjusted reference values is noticed. He added that proper evaluation of PLP to PA ratio is also crucial. Dr Mughal cautioned that classical changes may not be present in juvenile forms, necessitating additional care while evaluating the patient. The management of HPP and the role of appropriate calcium supplementation according to RDI and age was discussed. Prof Mughal opined that higher doses of vitamin D must be avoided as they may increase the tendency for hypercalcemia, hypercalciuria and subsequent nephrocalcinosis. He stated that bisphosphonates will disrupt proper mineralization in these patients' case. He summarized HPP as a rare inborn error in the bone metabolism caused by genetic mutations inactivating TNALP which leads to increased PPI, an important inhibitor of mineralization of the bones and teeth. He emphasized the need to be aware of the types of HPP and the wide diversity of clinical picture among them.

International Trials on HPP Treatment – Prof Nick Shaw

Prof Shaw's presentation focused on the trials in perinatal, infantile and juvenile HPPs. He stated that Asfotase alpha is a human recombinant tissue nonspecific form of ALP, which has domains linked to the IgG and the bone targeting domain, a deca-aspartate peptide. It is administered subcutaneously and the current standard is 3 times in a week. He discussed the clinical trials, ENB 002-08 and ENB 003-08 which studied the efficacy of Asfotase alfa in young children with life-threatening perinatal and infantile HPP. The trial design, inclusion criteria and assessment parameters were discussed in detail. Data from a phase-II, open label study was presented, in which patients were given IV AFA followed by subcutaneous dose in the initial phase lasting 6 months, and an extension phase which lasted up to 3 years. The median age of the cohort was 30 weeks. The radiographic global impression of change was assessed by 3 independent blinded assessors. The radiological changes over the 3 year's trial period and the RSS (Rickets severity scale) were assessed, which showed steady improvement over the trial period. The pre-treatment and post-treatment radiological images were discussed, including x-rays revealing the progression of the patient through the treatment course. Most of the cohorts required some form of respiratory support and over the trial period, the cohorts came off the support and at the end of the trial only one child required respiratory support in the form of oxygen. The adverse events, AE visits, and injection reactions were discussed. Dr Shaw pointed out that very few serious adverse events were reported and that the overall survival rate with AFA therapy was 90%. He stated that despite demonstrated efficacy and tolerability in prenatal and infantile HPP, there was no reduction in the risk of craniosynostosis. The second set of studies, ENB 006-09 and ENB 008-10, was done in juvenile and infantile HPP patients who survived beyond 5 years of age against historical controls of the similar age group with untreated HPP. The initial 6-month randomization phase was followed by an extension phase up to 3 years. The studies were conducted in the age group 5-12 years and the median age was

8.6 years. The key inclusion and exclusion criteria were discussed. The cohort consisted of 12 patients against 16 historical controls. They all could walk only 25% of what was expected of a child of similar age. The radiographic changes and RSS Scores were assessed and both these showed dramatic change in the first 6 months and then steady improvement until the end of the trial indicating healing of the rickets. The 6-minute walk test (6 MWT) was assessed at different stages, and it showed an improvement from 61% to 86% in the first 6 months. BOT-2 test (Bruininks-Oseretsky Test of Motor Proficiency) for strength and agility was studied and showed steady improvement. The running ability of the cohorts also showed significant improvement. The radiological changes were quite significant and showed steady improvement. The adverse events and injection reactions were discussed. Most of the adverse events reported were respiratory in nature and there were no serious adverse events. The survival data illustrated significant improvement compared with the controls. Prof Shaw concluded that data from clinical trials demonstrates that Asfotase therapy in HPP significantly improved the bone mineralization and muscle strength.

Regional Experience in HPP – Prof Moein Alsayed

Prof AlSayed's presentation focused on the genetic aspect of the disease and also discussed the clinical experience from KSA. He said that from the genetic point of view, HPP presents a spectrum of disorders ranging from mild to severe and the inheritance patterns vary from autosomal recessive, autosomal dominant and that sometimes recessive and dominant variants occur together. He stated that a working knowledge of inheritance patterns is required to pinpoint the genetic disorder when the patient presents to the clinic and that the most common genetic variant in HPP was the recessive disorder. He also pointed out that the differential diagnosis is vital in HPP and that genetics play a major role in this. Prof AlSayed presented different scenarios of inheritance including x-linked, autosomal recessive & dominant variants and discussed the inheritance patterns in these scenarios. He discussed *de novo* and germline mutations with variable expression and decreased penetrance and noted that *de novo* mutations have not been detected in HPP as yet. He opined that the only way to confirm decreased penetration is by molecular testing. He mentioned that consanguinity and lack of genetic counseling is a major cause for the prevalence of genetic disorders and repetition of founder mutations in the region. The various genetic expressions in HPP including the dominant, recessive and dominant negative types were discussed. He mentioned that genetically, a first cousin is a third-degree relative and noted that this degree of relation is important in explaining the genetic inheritance of diseases. He discussed about a study undertaken in KSA, where they screened 700 newborns for 16 genetic diseases and founder mutations and results were comparable with the similar studies in other countries in the gulf region. Prof AlSayed pointed out that the prevalence was at least 4 times higher compared to global statistics. He talked about the role of founder mutations in explaining the prevalence of HPP in the region and mentioned about the 2 novel mutations, in EXON 3 & 6 associated with HPP. He also discussed other possible pathogenic mutations which are currently being evaluated to ascertain if they are founder mutations. He talked about molecular genetic testing for HPP and said that to genetically confirm HPP, the recessive form by an allele pathogenic mutation and dominant form by a heterozygous pathogenic mutation should be reported. He stated that the most common method used was sequencing, and discussed the different methods of sequencing including single gene testing, gene panels, or whole exon sequencing. He said that negative sequencing doesn't confirm the absence of disease and have to do further deletion-duplication analysis to identify any mutations missed by sequencing. WGS was discussed as the option if the other genetic tests fail to identify the mutation and noted that WGS combines the benefits of both sequencing and deletion/duplication. He stated that the disease can be diagnosed based on the clinical, biochemical and radiological profile in patients who have the recessive form of HPP, and added that genetic sequencing should not delay the initiation of therapy. He said that 95% of cases, particularly from the European region, will have a mutation which can be identified by sequencing. He added that deletion/duplication is rare in HPP. He presented data from the University of Versailles which identified various mutations and also discussed the 5 typical variants reported in sequencing. He also talked about the ongoing Saudi Genome Project which aims to sequence all genomic variants and the allele frequency in the population. He discussed the limitations of sequencing reviewed the causes of 'inability to detect'. Prof AlSayed presented the cases of 4 patients with HPP and craniosynostosis. The pre- and post-enzyme replacement therapy (ERT) x-rays showed significant radiological improvement over the years. He discussed the significance of monitoring for nephrocalcinosis which lead to renal failure later in life. He emphasized the importance of early treatment in these patients and noted that even though mineralization continues to improve with late initiation, some changes such as scoliosis may be irreversible. He opined that though ERT improves the general wellbeing, mineralization and functionality, patients may remain fragile and need multidisciplinary care and follow-up. He said that ERT has no impact on craniosynostosis and needs an experienced neurosurgeon for management of chronic and severe headaches. He concluded the presentation stating that the long-term prognosis of these patients remains unclear; however, to prevent complications, early intervention is very important.

Highlights

1. Low ALP is one of the hallmarks features of HPP.
2. The efficacy and safety of Asfotase in the management of HPP has been demonstrated in several clinical trials.
3. Bisphosphonates will disrupt proper mineralization in HPP.
4. Biochemically, it is important to measure ALP accurately and in reference to the age and gender adjusted values.
5. Asfotase alfa normalizes the mineralization and muscle weakness in HPP patients.
6. It is important to look at the whole picture including the patient's history, family history, clinical manifestations, complete biochemical profile, and radiological patterns to confirm the diagnosis.

7. Misdiagnosis could be the reason for low incidence of the disease in KSA.
8. Long-term prognosis of patients remains unclear; however, to prevent complications, early intervention is very important.

Session IV - Diagnostics & Case Scenarios in HPP

Chairpersons: Prof Zulf Mughal and Dr Saif Al Yarubi

Clinical Case Scenario I – Prof Abdelmoein Al Agha

Prof Al Agha stated that HPP is very rare and hence awareness is very important in the proper and early diagnosis and management of the disease. His presentation focused on a case of HPP which was misdiagnosed and treated as nutritional rickets by peripheral centres. He said that on presentation with skeletal deformities, the pediatricians hastily go for rickets considering it as the only bone metabolic disorder unlike the pediatric endocrinologists. He noted that misdiagnosis could be one of the reasons for low incidence of the disease in KSA. He pointed out that the hospitals in KSA have now started to adjust the ALP ranges to age and gender as is the recommended standard and pointed out that the wrong reference ranges for ALP which existed until now could be another reason for low incidence of diagnosed HPP. He presented the case of a child who presented at 1 year 9 months of age, started to exhibit signs of skeletal deformity from the age of 9 months. The skeletal changes were like rickets but there were no apparent benefits despite receiving high doses of vitamin D and calcium since one year. Dr Al Agha stated that the patient's situation had worsened over the year. The child was born out of a consanguineous marriage and had one sibling with similar symptoms who was undiagnosed and passed away at 2 years of age due to respiratory failure. He was of short stature, had delayed eruption of teeth, bowing of legs, and gross motor development was also delayed. Biochemical profile revealed slightly high Ca, high phosphate, Vit D, low PTH, and low ALP, even when the value was not corrected to age and gender. He re-emphasized the need for correcting ALP reference to age and gender so as not to miss the diagnosis. The patient was diagnosed as HPP and managed with AFA. He stated that the patient responded well and was able to stand within 5 months into AFA therapy. He discussed the high prevalence of rickets in KSA and the importance of proper differentiation of diagnosis between metabolic bone disorders, like nutritional and hereditary rickets, OI, skeletal dysplasia and HPP. He briefly discussed the pathophysiology of HPP and the classifications of HPP. He noted that there are more than 300 mutations identified associated with HPP and stated that low ALP is one of the persistent hallmark features of HPP and emphasized the importance of low ALP levels as the chief indicator which supports the genetic findings. He pointed out 'treating symptoms and complications' rather than definitive treatment of the disease as one of the main challenges and noted that wide variation in presentation and sensitivities increase the chances of misdiagnosis. He opined that perinatal form as the most lethal form of HPP. Dr Al Agha concluded the presentation reiterating the importance of ALP levels and called for more research on HPP to support the clinicians. He talked about the burden of the disease on the patient, family and the healthcare system. He said that until 2015, there was no definitive treatment of the disease but only conservative management. His take home message was to increase the awareness about the disease among pediatricians, family physicians as well as among pediatric endocrinologists to prevent misdiagnosis and ensure that all regions have age and gender adjusted ALP references range.

Clinical Case Scenario II – Dr Aisha Al Sinani

Dr Al Sinani presented 2 cases of HPP from Oman. The first case was a 10 years old child who presented with a history of recurrent hospital admissions for respiratory problems, muscle weakness and rickets-like skeletal deformities, and lower growth percentile. She had good dentition. The biochemical profile showed with normal Calcium and Phosphate, and very low ALP. She was diagnosed as HPP and started on AFA therapy, responded well and the ALP levels increased. The pre and post therapy x-rays were presented and discussed. The skull x-rays didn't show as much improvement as the long bones with therapy. Dr Al Sinani presented the case of a 5-year-old boy who was diagnosed with HPP at 8 months and is the sibling of the above case. He had an early diagnosis and early initiation of therapy with Asfotase. On presentation, he had low ALP, normal calcium, phosphate and vitamin D. The x-ray showed rib cage deformity. He is currently into the 14th month of enzyme replacement therapy without any apparent side effects. His x-rays showed good improvement in mineralization and even the skull x-ray showed better progress in him than the sister, probably due to early initiation of treatment. Genetic counselling of family showed homozygous recessive mutation.

Clinical Case Scenario III – Dr Fatima Al Jasmi

Dr Al Jasmi presented the case of a new born who was diagnosed in-utero with bone anomalies and reduced fetal movement. The mother was 39 years old and union was consanguineous. The child was born at term with a narrow rib cage and required delivery with suction. She developed respiratory distress which worsened within 4 days and was connected to the ventilator and required mechanical ventilation for one month. She was in the NICU for 2 months and was discharged on 2 litres of oxygen and nasogastric tube. Genetic analysis showed heterogeneity in parents as well as low ALP on biochemical profile and both parents had history of juvenile fractures. Mother has history of multiple pre-term abortions. Clinical features showed low set ears, short limbs with bowing, narrow chest and grossly delayed motor skills. Biochemical analysis revealed low ALP. The patient was diagnosed with HPP which was confirmed genetic sequencing. The patient was admitted multiple times for respiratory distress. The mother heard about an ERT trial going on and discussed with doctors and got her involved in the trial. The patient showed clinical improvement and was no longer considered a "failure to thrive". Dr Al Jasmi stated that the patient was not admitted to PICU after therapy started and added that she is the oldest patient with prenatal HPP on ERT. She had craniosynostosis which was managed by the neurosurgery team and the intracranial pressure was managed by surgery. The patient was treated with surgeries by orthopaedic team for management of fractures and scoliosis. She was managed by a multidisciplinary team including an ENT

specialist for hearing loss, pulmonologist for pulmonary function, nephrologist for the nephrocalcinosis which has improved with ERT, and a dentist. The rehabilitation team was actively involved in her management and genetic counselling was done for the family.

Summary of Discussions

A single experience was shared where craniosynostosis showed improvement with AFA therapy as reported by a neurosurgeon in contrast to the studies which have shown that AFA has no impact on craniosynostosis. The role of vitamin B6, PA & PPI levels was discussed and it was noted that that PA and PPI are still not available in many centers. Prof Mughal said that generally there is adequate intake of dietary Vitamin B6 and suggested supplementation with 150% of the actual nutritional requirement. So, the vitamin B6 is not a reliable indicator of actual vitamin B6 levels. PA is very important as even with the dietary intake, the PA levels are not affected in the absence of ALP. However, sampling is very important in the PPI & PA as the assay has to be done on RBCS. The samples should be EDTA and should not be exposed to sunlight. Prof Mughal noted that the biochemists report it as a straightforward assay, which can be established in any lab in the region. The relevance of zinc measurement was discussed due to potential effect on ALP levels. Prof Mughal pointed out that zinc can affect ALP only at extremely low levels and that this scenario may not be relevant in this part of the world. There was a discussion on which specialty should lead the management of HPP patients. All agreed that HPP should be essentially managed by a multidisciplinary team comprising of several specialties. The need for a tertiary center with all specialties and good therapists for rehabilitation were highlighted. There was further discussion on the importance of follow-up with ophthalmology and ENT as these patients frequently have vision and hearing problems. However, it was concluded that levels of ALP is not the direct cause of these vision or hearing problems. The importance of genetic screening was discussed. It was noted that there is wide variation in the biochemical and radiological profile of these patients and genetic analysis do not always confirm a mutation. However, there was a general agreement among the speakers that low ALP, adjusted to age and gender is the hallmark indicator and even if the genetic analysis return negative, further genetic counselling and investigations including WES and WGS should be pursued, but treatment should be initiated without waiting for genetic confirmation if the clinical, biochemical and radiological profile points towards HPP.

Highlights

1. Vitamin B6, PA and PPI levels are important but assessments for PA and PPI are still not available in many centres.
2. HPP should be managed by a multidisciplinary team comprising of several specialties.
3. Rickets is highly prevalent in KSA and proper differentiation of diagnosis between metabolic bone disorders, like nutritional and hereditary rickets, OI, skeletal dysplasia and HPP is essential.
4. Rickets is highly prevalent in KSA and proper differentiation of diagnosis between metabolic bone disorders, like nutritional and hereditary rickets, OI, skeletal dysplasia and HPP is essential.
5. Low ALP, adjusted to age and gender is the hallmark indicator and even if the genetic analysis returns negative, further genetic counselling and investigations including WES and WGS should be pursued.
6. Low ALP, adjusted to age and gender is the hallmark indicator and even if the genetic analysis returns negative, further genetic counselling and investigations including WES and WGS should be pursued.
7. Zinc can affect ALP only at extremely low levels and measurement of zinc in the body may not be relevant in this.

Day 2

The second day of the meeting focused on nuclear imaging in osteoporosis, calcium disorders and other metabolic bone disorders. The role of sub-specialties in metabolic bone disorders was also discussed.

Session V - Nuclear Imaging and Osteoporosis

Chairpersons: Prof Zulf Mughal and Dr Zaidan Al Mazidi

Dexa Scan: Utilization in Bone Diseases – Prof Nick Shaw

Prof Shaw started the presentation by stating that bone density by DEXA scan is not the only determinant of bone fracture risk. He added that bone strength is determined by the amount, quality and distribution of the bone. He pointed out that DEXA scans can only measure mass, area and geometry, but it cannot measure material density, volumetric bone density, cortical thickness and bone distribution. He also stated that projection errors due to the inability to measure volumetric bone density, and the resultant dependence on size is a shortcoming associated with DEXA scans. The large variation between body sizes among children of the same age, which necessitates adjustments for body size also adds to the limitations. Prof Shaw continued to explain the steps to adjust using BMAD and the equation used to do that. He also elucidated the effect of puberty on bone density and the relation between steroid treatment and loss of mobility in boys with Duchenne Muscular Dystrophy. Prof Shaw talked about the definition of osteoporosis and how that definition had been revised in 2013, stating that fractures are critical for the diagnosis of osteoporosis in children including vertebral compression fractures. He then compared the relative merits of the vertebral fracture assessment (VFA) and spine radiograph and stated that VFA is better because; it subjects the patient to less radiation dose, shows whole spine without any magnifications, allows improved thoracic visualization, vertebra identification, is useful in detecting asymptomatic vertebral fractures which can co-exist with normal bone density, and availability at point of care. He continued to discuss the case scenarios of few patients diagnosed to have osteoporosis using the VFA scan. Prof Shaw also discussed the ALSPAC prospective fracture study and the QCT (quantitative computed tomography) studies in relation to

fracture. Prof Shaw then elaborated a protocol for a prospective study relating bone density to fractures and outlined the tests conducted at baseline and those carried on in the follow-up. He then talked about incident fracture and its association with reduced bone density, bone diseases, physical activity and steroid treatment. Prof Shaw concluded his presentation by highlighting the importance of using different imaging modalities to provide a more comprehensive analysis.

Non-Oi Osteoporosis: Case Scenarios and Treatment – Dr Walid Kaplan

Dr Kaplan started his presentation by discussing the process of bone remodeling and duration of the remodeling cycle. Understanding the relationship between physical activity and the strength of the bones is acutely pertinent, he said, and discussed the results of a clinical trial which was conducted to assess the effect of physical activity on the bone. Data from the study revealed that weight bearing physical activity improves bone density and quality but questioned if immobilization does the opposite. Data from another study that included 38 patients with hemiplegia and aimed to answer the question were reviewed. He stated that in the study BMD was significantly less in the paretic sides of the femoral neck and radius which indicated that immobilization does decrease the bone density. Dr Kaplan then talked about the relation between cerebral palsy and osteoporosis and he mentioned the study to measure BMD in patients with moderate to severe cerebral palsy which demonstrated that while 77% of the patients had low BMD, BMD was even lower in patients with full immobilization or older patients. He also discussed the relationship of bisphosphonates and cerebral palsy (CP) and reviewed the results of a study which evaluated the effect of pamidronates in spastic quadriplegic cerebral palsy patients. Nine patients with low BMD were treated with pamidronate for 12 months showed improvement, however their BMD returned to pre-treatment level about 2 years after treatment. He added that there was no fractures reported and the fracture rate dropped from 30.6% to 13.6% which is equivalent to more than 50% reduction in the fracture rate. He also reviewed data from a study with zoledronic acid in CP patients with low BMD and stated that patients showed improvement and reported no fractures during the follow-up period (mean 3.9 years) however 30% of the patients developed fever. Finally, he talked about residronate and how its combination with alfacalcidiol was superior to the alfacalcidiol treatment alone. Based on these observation, he stated that bisphosphonates can improve BMD and decrease bone fracture rate, and may be considered on compassionate grounds if the treatment of the underlying cause wasn't effective. Dr Kaplan concluded his presentation by mentioning the different levels of prevention and the additional investigations needed to be considered in patients with osteoporosis.

Idiopathic Juvenile Osteoporosis; Interesting Presentation – Dr Fahad Al Juraibah

Dr Al Juraibah presented a case of an 11-year-old who had lower back pain of increasing severity for over a year. There was no history of fractures and the medication history, family history and medical history were unremarkable. On the Tanner assessment of pubertal development, he was Tanner stage 2 for gonadal development. His radiograph revealed evidence of decreased bone density with no evidence of fracture, and skeletal survey showed diffuse severe osteopenia. His lumbar spine DXA-Z score was -2.38 SD, he had no significant findings in his lab investigations, and by exclusion he was diagnosed with idiopathic juvenile osteoporosis. Dr Al Juraibah reviewed the definition of osteoporosis and the difference between adult and pediatric osteoporosis. He also reviewed the components of BMD assessment which included DEXA scan, quantitative CT and bone biopsy, and then talked briefly about the etiology of osteoporosis. He also discussed idiopathic juvenile osteoporosis and stated that pathophysiology is still unknown and is characterized by dysfunction in cancellous bone formation. He stated that the roentgenogram shows biconcave vertebrae, vertebral compression and metaphyseal fractures and that the mean age of presentation is 7 years. Dr Al Juraibah concluded his presentation by stating that the disease is self-limiting and it resolves spontaneously by puberty although spine deformities may persist.

Interesting Variant of Bone Disease: Case Scenario – Dr Mohamed Al Dubayee

Dr Al Dubayee presented a case of a 13-year-old with normal activity and negative family history. Her height was below the 5th percentile and weight within 10-25 percentile and Tanner stage 1 of puberty. Her lab investigations were normal, however, her growth hormone stimulation test peak was low. MRI of brain which did not reveal an apparent abnormality, however, her skull x-ray showed translucencies. The patient's father refused biopsy of the skull stating that his brother and his father have the same skull abnormalities (indicating a possibility of the disease being an autosomal dominant). Her skeletal survey showed osteopenia however there was no fracture, thus she was diagnosed to have Calvarial doughnut lesions and osteoporosis, which is a disease with no pathogenic mutations nor known pathophysiology, however it is characterized by the distinctive X-ray translucencies in the skull, elevated serum ALP and multiple fractures. The speaker discussed the management options in patients who present with the features illustrated in the case scenario. He emphasized that it is indeed very essential to be aware of signs of symptoms and suspect the diagnosis in a timely manner for efficient management of the patient.

Diagnostic Signs in an Interesting Case – Dr Dina Ramadan

Dr Ramadan discussed a case of 3M syndrome, whose parents were 1st degree cousins. At the age of 1.4 years, she was started on growth hormone after which there was an improvement in height. Molecular investigations revealed a homozygous mutation in OBSL1 gene (truncated nonfunctional OBSL1 gene), based on which she was diagnosed with 3-M syndrome. Dr Ramadan listed the clinical features which included frontal bossing, anteverted tip nose, triangular face, hypermobile joints and prominent heels. Radiographic features such as long slender bones and tall vertebral body and genetic characteristics such as mutations in

either CUL7 (65%), OBSL1 (30%) and CCDC8 (5%) were discussed. Dr Ramadan mentioned that studies showed that patients with Cul7 are the shortest while patients with CCDC8 may be relatively taller. She discussed the case of another patient who had dolichocephaly, prominent ears, mid-facial hypoplasia, anteverted nose and a short neck. His lab investigations revealed primary IGF1 deficiency and so he was treated with IGF1 (Increlex) twice daily. She mentioned that the improvement wasn't significant despite treatment with IGF1 and added that subsequent molecular testing showed a homozygous mutation in OBSL1 gene, which resulted in a diagnosis of 3-M syndrome. The third case Dr Ramadan discussed had similar features and investigations as the previous one, however, her molecular testing showed mutation in the CUL7 gene. Dr Ramadan stated that 3-M syndrome is a form of skeletal dysplasia which can be confused with various disorders of growth hormone axis. 3 M syndrome causes infertility and gonadal dysfunction, thus it should be identified and treated early. She added that if the patient is not responsive, rhIGF-1 therapy should be considered but not necessarily effective.

Summary of Discussion

Steroid effects on bone health were discussed. Asthma and the use of inhaled corticosteroids effect on growth should be beard in mind. It was highlighted that inhaled corticosteroids may not influence fracture risk or bone density and there is a lack of evidence of increase in fracture risk with the use of inhaled corticosteroids.

The effect of long term use of bisphosphonates in cerebral palsy patients was discussed and the need for a booster dose 3-4 years after initial treatment for 15 month was highlighted. It was generally agreed that the long-term use of bisphosphonate is not favorable and they should be administered for a predefined finite amount of time. Whilst on bisphosphonates, patient can be maintained on calcium and Vitamin D supplements. Data from a study which demonstrated that treatment with pamidronate for 12- 15 months is associated with a fracture free interval for 5 years was discussed. In light of this, it was recommended that zoledronic acid should be used for 1 year and that it can be restarted if a fracture appears. In this regard, it is shown that the utility of measuring bone density in these patients is low and difficult to assess. In relation to the presentation of the 3M syndrome presented by Dr Ramadan, some participants suggested that dysplasias are not the only cause of short statures, and that patients with such conditions may respond to GH treatment if started at a very early age. Dr Ramadan concurred with that observation stating that 3-M fits that criteria and mentioned the importance of diagnosis in determining the doses and the importance early treatment. She highlighted that there is a genetic correlation with the response of growth hormone treatment. In response to a query pertaining initiation of treatment, prophylactically or after incidence of a fracture, in CP patients with a high risk of osteoporosis, it was stated that treatment should be initiated prophylactically and ascertain pathological fractures if warranted with a DEXA scan. However, this idea was debated by other attendees who argued that even though 77% of CP patients have low bone density, only 4% develop fracture thus routine prophylactic treatment might be unnecessary. The importance of communication between physicians to concur on standardized recommendations if not guidelines was highlighted. A detailed discussion was run about interpretation of BMD. Ways to adjust BMD for size was enquired about particularly if the adjustment could be done automatically through incorporation in software. A number of methods for size adjustment were discussed. These include the use of the areal density and width of the lumbar spine. Correction for height or body mass can be done manually. It was recommended that a reference value must be determined for the population in the Middle East. Assistance in this task was offered by Prof Shaw and Mughal for the purpose of development of a database and reference values. The role of bone biopsies in cases of idiopathic juvenile osteoporosis was enquired about. According to the international society of bone densitometry, bone biopsy has no role in diagnosis. Assessment of bone density using DEXA should suffice in this condition. However, bone biopsy might show the low bone turnover which is characteristic of this disorder. Whole genome sequencing should also be considered.

Highlights

1. Different imaging modalities should be used judiciously to provide a more comprehensive analysis.
2. Least significant change (LSC) is very important but it should be measured after 6 months to a year.
3. Long term use of bisphosphonates may not have any significant advantage in cerebral palsy patients. They should be administered for a predefined finite amount of time and may be given concurrently with calcium and Vitamin D supplements.
4. Treatment can be initiated prophylactically in CP patients with a high risk of osteoporosis. However, since only 4% from among the 77% of CP patients who have low bone density, develop fracture, prophylactic treatment with bisphosphonates needs to be further evaluated.
5. Standardized recommendations for diagnosis and guidelines for treatment are necessary to facilitate homogenous treatment practices in various countries of the region.
6. Reference values for BMD must be determined for the population in the Middle East.
7. In non-OI osteoporosis bisphosphonates can improve BMD and decrease bone fracture rate.

Session VI - Calcium Disorders/Hyper & Hypocalcemia

Chairpersons: Prof Nick Shaw and Dr Walid Kaplan

Diagnostic Approach to Calcium Disorders – Dr Sarah Ehtisham

Dr Ehtisham discussed calcium homeostasis, the role of PTH, measurement of corrected and ionized calcium, effect of ionized calcium on seizures, and the clinical features of hypocalcemia. She

showed pictures demonstrating Chvostek's sign and Trousseau's sign and highlighted the importance of magnesium levels testing and other key investigations. She discussed the categories of hypocalcemia: hypocalcemia with low PTH, hypocalcemia with normal PTH and hypocalcemia with high PTH. She talked briefly about each, and discussed the management suggesting that hypocalcemia with normal PTH might not need treatment, however in patients with clinical conditions such as convulsions, IV treatment with calcium gluconate is needed. She opined that in non-emergency situations oral calcium supplements, PHP, vitamin D analogues and recombinant PTH are used. She also highlighted the importance of maintaining the calcium excretion cycle to avoid hypocalciuria. Dr Ehtisham also discussed hypercalcemia, and the key investigations. She classified hypercalcemia by PTH levels - low, normal or high, and elucidated the treatment of hypercalcemia which included promoting mobility and reducing calcium intake, decreasing calcium absorption by glucocorticoids, reduce PTH secretion by cinacalcet and parathyroidectomy.

Case 1 (Hypercalcemia) – Dr Amir Babiker

Dr Babiker presented a case of a 21-month-old patient with Sanjad-Sakati Syndrome (SSS), with a narrow face, microcephaly, large ears and thin lips, long philtrum and with history of hypocalcemia. Molecular testing revealed a mutation in *TBCE* gene which is characteristic for this disease. He elaborated the definition of SSS, and explained its clinical presentation which included recurrent chest infections which could lead to death, ear infection and reduced number of T-cell subsets, which may be subsequent to functional hyposplenism and impaired polymorphonuclear call functions. He discussed the treatment which included calcium supplements and active vitamin D supplements, low phosphate diet and treatment of the intercurrent infections. He also discussed the complications of the disease which may include the kidneys and hypocalcemia during intercurrent infections. He stated that SSS has a mortality rate of 27% and that rare cases survive up to 18 years. He also discussed other issues associated with the condition which include congenital hypoparathyroidism, growth failure, global developmental delay, seizure disorder and congenital hypothyroidism, dense nephrocalcinosis and unexplained hypercalcemia. Dr Babiker discussed another case who was diagnosed with hypoparathyroidism, was treated with alfacalcidol and oral calcium supplements, and was lost to follow-up for 1 year. During that period, he developed intercurrent illnesses of profound low Ca which required infusions of Calcium, he developed hypercalcemia which persisted despite the discontinuation of IV Calcium. He was transferred to another hospital, and remained hypercalcemic. His ALP remained the same, fluctuations of phosphate, vitamin D were within normal limits, his PTH remained low, urine calcium creatinine ratio was high and he had dense nephrocalcinosis. Dr Babiker talked about the possibilities for this case which were either overtreatment, oversensitivity to treatment, other pathology e.g. adrenal insufficiency which was ruled out due to normal level of ACTH, partial hypoparathyroidism or medication side effects such as valproic acid and its effect on decreasing bone density. He added that the Ca supplements were discontinued for the patient, and were reduced after he developed hypocalcemia 2 weeks later. He pointed out that the patient developed hypercalcemia again, so he was started on recombinant parathyroid hormone(r-PTH) teriparatide. His MRI showed a small pituitary, low IGF-1, he was started on cortisol to be taken with intercurrent illnesses, yet after treatment he showed high levels of T4 and TSH, the patient was referred back to the hospital, he didn't need Ca supplements for 1 year, the further treatment plan for this patient was to optimize hypoparathyroidism treatment, do Synacthen test and to be started on GH trial in the future. Dr Babiker talked about nephrocalcinosis in hypoparathyroidism and its relation to intercurrent illness and prevention. He also elaborated on the role of cortisol on Ca level and concluded his presentation by talking about the use of teriparatide treatment in children.

Case 2 (Hypercalcemia) – Dr Saif Al Yarubi

Dr Al Yarubi discussed a case of a 33 weeks old patient, who was admitted in NICU and on the 1st day of admission had multiple subcutaneous nodules on trunk and limbs, hypotonia with poor feeding, anemia that required blood transfusion 3 times, septicemia. The patient had severe metabolic acidosis, high ALP and was resistant to bicarbonate treatment. Her blood picture showed high calcium, and was given Policitra 2 ml QID after correction of the acidosis. Frusemide and hydrocortisone were given for the hypercalcemia. On day 2 after admissions, her blood PH improved, but she was severely anemic. Her echocardiogram showed a tiny PDA and a small PFO. Her PTH and vitamin D were very low. On the 3rd day of admission, lactoacidosis increased, and had hypothermia, and edema. On the 5th day, she had worsening of the generalized edema and went into acute renal failure. She progressed to have oral and nasal bleeding and bradycardia within 5 min asystole. The diagnosis of subcutaneous fat necrosis was discussed and its clinical presentation, histopathology and pathophysiology were detailed.

Dr Al Yarubi discussed a case of another patient born at 36 weeks to consanguineous parents. She had a high ALP, high calcium, low phosphate. She had intrauterine growth retardation, subtle dysmorphism and craniosynostosis. The cardiovascular examination revealed a pan systolic murmur and her parathyroid hormone was elevated. Skeletal survey showed diffuse osteopenia and thinned cortical bone. The differential diagnoses considered were severe neonatal hyperparathyroidism, familial hypercalciuric hypercalcemia or William syndrome. Genetic analysis showed a mutation in the *CASR*. The patient underwent surgery later and her PTH levels remained within the normal range 2 years after surgery.

Case 3 (Hypocalcemia) – Dr Elham Al Amiri

Dr Al Amiri presented a case of an 8 years old patient with convulsions, stiffness of the back and mouth frothing with history of oral candidiasis. The patient was drowsy and jittery. His lab results showed low Ca levels, high phosphorus, magnesium in the lower end of the range, low PTH. He was treated with IV calcium, IV ceftriaxone and was discharged on oral calcium supplements. The patient was diagnosed by autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), which is diagnosed by presence of 2 out of the three components of the classical

triad: Hypoparathyroidism, chronic mucocutaneous candidiasis and Addison disease. The patient then underwent the Synacthen test which was normal at time of discharge and after 6 months. The patient returned at age of 12 with the same symptoms, and tests revealed adrenal insufficiency. Treatment was initiated with hydrocortisone tablets and fludrocortisone. He was readmitted at age of 13 with adrenal crisis, with no signs of puberty, his blood tests showed low calcium levels and ACTH was high, so his treatment was adjusted accordingly. Dr Al Amiri discussed the APECED disease elaborately and the defect in the *AIRE* gene that is involved with it, its prevalence, pathophysiology and explained more about the triad and other manifestations, and how autoantibodies could give a more certain confirmation or exclusion of the disease than gene analysis.

Case 4 (Hypocalcemia) – Dr Adil Al Amry

Dr Al Amry presented the case scenario of a 3 months old patient with IUGR and was the offspring of consanguineous parents. His physical examination showed triangular face with deep set eyes, small hands and feet, hypotonia, convulsions, delayed development dysmorphism and failure to thrive. His lab investigations revealed low levels of calcium, low PTH, and high phosphate which indicated hypoparathyroidism. Her MRI showed microcephaly and craniosynostosis, and molecular testing showed mutation in TBCE which confirmed a diagnosis of SSS. Dr Al Amry discussed the management and treatment of the patient and the challenges of the disease which included adjusting the calcium and the Ca/creatinine ratio, history and prevalence of SSS, and clinical features. He compared the disease and Di Goerge's syndrome. Dr Al Amry also discussed Kenny Caffey syndrome and the difference in the dysmorphic features. He compared the clinical findings between Kenny Caffey syndrome and SSS. The treatment of Kenny Caffey syndrome with calcium and alphacalcidol along with controlling the hyperphosphatemia, and managing the generalized calcification also were discussed.

Summary of Discussion

The discussion was started by a query about the ideal serum calcium to maintain in patients with high PTH e.g. pseudohypoparathyroidism and whether keeping calcium level at the lower limit of normal is preferred. It was stated that urinary findings may be more pertinent in such clinical situations. It can be very difficult to lower the PTH and get normal levels of calcium in these patients. The yield of positive *AIRE* gene in patients with typical APS type 1 was discussed and it was highlighted that the genetic test could still be negative in presence of the classical syndrome and treatment should not be delayed in the presence of the negative testing. The role of surgical management of parathyroid disease was discussed. Parathyroidectomy with forearm tissue implantation can be useful as further resection can be done with easy access should the hormone level remained high. The importance of a referral mechanism was reiterated by the speakers who highlighted the importance of having a database of all the physicians name and specialties to allow assistance to access the database and decide on referral.

Session VII - Role of Subspecialists in Metabolic Bone Disorders

Chairpersons: Dr Asmahane Ladjouze and Dr Haya Al Khayyat

Role of the Paediatric Orthopaedic Surgeon – Dr Marc Sinclaire

Dr Sinclaire explained the Hueter-Volkmann, the Wolff's law and Delpech's laws which are related to the biomechanics of bone growth and modelling. He talked about the factors that affect the prognosis of bone deformities including the location of the angulation, distance to the growth plate, contribution of growth plate to growth, remaining growth potential and plate deformity (rotational deformity doesn't correct well). He stated that bracing or casting in rickets is not effective, and that spontaneous correction is needed if the varus /valgus deformity is under 15°. He also explained the temporary Epiphyseodesis procedure to avoid osteotomy and stated its advantages in that it does not correct long bones and can guide growth in the right direction. He explained the way to measure the degree of the deformity as the distance between the mechanical axis deviation and the center of the knee. He highlighted that osteotomy might be a better choice in the older patient and if the physician cannot follow-up with the patient. Dr Sinclaire discussed the treatment options in severe deformities such as temporary hemiepiphyseodesis (guided growth), which is a minor procedure with minimal morbidity and minimal risk on growth plate. However, he highlighted that it may not always be effective. He gave an overview of osteotomies in acute and gradual correction, and enumerated the indications of each and concluded the presentation by stressing on the importance of quality of bone in selecting the implants to be used, and emphasized that natural disease progression must always be in kept in mind while contemplating surgical interventions.

Role of the Paediatric Rheumatologist – Dr Khulood Khawaja

Dr Khawaja described the clinical scenarios where consultation may be sought from a pediatric rheumatologist. She illustrated case scenarios which warranted the expertise of a paediatric rheumatologist. The first case she described was that of a 12 years old patient who presented with deteriorating handwriting, increasing lethargy and background of type 1 diabetes. She stated that the patient had no movement in her wrists unless she had an injection, and was diagnosed with juvenile idiopathic arthritis. Dr Khawaja discussed another patient who was diagnosed with Juvenile systemic lupus erythematousis at the age of 6. She had 2 thromboses in her left leg and suffered an extradural hematoma. She was on long term steroid treatment and had severe lower back pain and short stature. Dr Khawaja mentioned that the 2 main problems for this patient were the active, poorly controlled disease and secondary complications due to chronic steroid treatment. Dr Khawaja described another case who presented with progressive weakness, deterioration in gross milestones, fatigability and lethargy. The patient's blood tests revealed raised liver transaminases (AST and ALT) and significantly high CK. Her chest X-ray showed signs of inflammation. Dr Khawaja stated that the patient was administered pamidronate as a regular treatment

every 3-4 months using the same guidelines as endocrinologists. The other clinical case Dr Khawaja presented was that of a patient who had pain in the right hip and knees, pain and swelling in the shoulder and clavicle. The patient was diagnosed with chronic multifocal osteomyelitis (CMO). She talked briefly about the clinical features, radiographic findings and treatment of CMO and pointed out that the diagnosis of these conditions requires awareness of the clinical characteristics and a high index of suspicion.

Role the Clinical Biochemist – Dr Abubaker Elfatih

Dr. Elfatih began his presentation by discussing the common laboratory findings (low phosphate and Vitamin D) in patients with hypophosphatemic rickets. He discussed renal tubular phosphate reabsorption – indications, formula as well as the most appropriate time to provide urine sample for the test. He also mentioned the evaluation procedure of TmP/GFR that provides diagnostic clues regarding renal phosphate transport. Dr. Elfatih discussed the formula used to measure tests for making a diagnosis of Fanconi's syndrome. Dr. Elfatih mentioned that 1,25 hydroxyvitamin D testing does not get insurance coverage. He pointed out that normal levels of 1,25 hydroxyvitamin D is not an indication to exclude deficiency of Vitamin D. Plasma PTH, serum calcium, serum phosphate and FGF-23 are related to 1,25 hydroxyvitamin D and hence should be measured at the laboratory. He opined that samples for testing 1,25 hydroxyvitamin D should be processed as early as possible due to its short half-life of 4 hours. He highlighted that LC-MS/MS remains the gold standard technique for measuring 25-hydroxy vitamin D2 and D3. Dr. Elfatih mentioned that early morning samples are preferred while testing for PTH.

Summary of Discussion

It was highlighted that there is a variation of 20% if PTH sample is tested at any point of the day. Regarding a query on the reference range for PTH with respect to serum and plasma, Dr. Elfatih replied that reference ranges exist while testing for either serum or plasma and he prefers to use two different reference ranges.

Highlights

1. Assessing the quality of bone is very important while selecting the implants.
2. The natural disease progression must always be in kept in mind while contemplating surgical interventions.
3. Conditions like Juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, and chronic multifocal osteomyelitis may require a paediatric rheumatologist as these conditions require awareness of the clinical characteristics and a high index of suspicion.
4. LC-MS/MS remains the gold standard technique for measuring 25-hydroxy vitamin D2 and D3.
5. Early morning samples are preferable for assessment of PTH.
6. Issues surrounding reimbursement for assessment of 1, 25 hydroxyvitamin D pose challenges.

Session VIII - Skeletal Dysplasias/Miscellaneous Bone Disorders

Chairpersons: Dr Ahmed El Awa and Dr Mohamed Abdulla

Miscellaneous Bone Disorders – Prof Zulf Mughal

Prof Mughal began his presentation by discussing the endochondral mineralization of the growth plate. He pointed out the importance of dietary calcium and its relation to Vitamin D deficiency. He stated that majority of the patients develop rickets when their calcium intake is low. However, he noted that patients with rickets were allergic to dairy products. Prof Mughal discussed the case of a patient who was diagnosed to have Vitamin D deficiency as well as allergy to dairy products. His daily diet included pasta, rice, potatoes and small amounts of meat as a result of which the patient developed severe calcium-deficiency rickets. The patient responded well to calcium supplement therapy. Prof Mughal presented a case of a female child who was diagnosed with upper respiratory tract infection. She developed right-sided Bell's palsy following 4 weeks of treatment for upper respiratory tract infection. This patient developed stroke with asymmetric spastic quadriplegia as well as visual impairment. Genetic testing revealed compound heterozygous hepatic ATP binding cassette subfamily C member 6 (ABCC6) confirming the diagnosis of generalized arterial calcification of infancy (GACI). The patient responded well to treatment with Etidronate. Prof Mughal discussed the presentation of this patient's brother who had calcified kidneys on nuclear imaging which also showed calcifications in the skull. Genetic testing revealed mutation similar to his sister and hence responded well to therapy with bisphosphonates. Prof Mughal discussed the case presentation of two non-identical twins (male and female) who presented with heart failure associated with calcifications of coronary artery and aorta. Both twins were treated with pamidronate; however, the male sibling died following 3 months of therapy whereas the female sibling is alive and did not need further therapy with bisphosphonates. Prof Mughal discussed the pathophysiology of GACI and laboratory findings. He focused on osteopetrosis and its types – osteoclast-poor osteopetrosis and osteoclast-rich osteopetrosis. Osteoclast-poor osteopetrosis has defective osteoclast numbers whereas osteoclast-rich osteopetrosis has defective acidification of the extracellular space between ruffled border of osteoclast and the bone surface.

Prof Mughal presented an interesting case of a female child who was diagnosed with osteopetro-rickets. This patient had renal tubular acidosis, cerebral calcifications, proximal femoral fracture, mental retardation and was short in stature. Molecular testing showed inactive mutation of the gene coding for carbonic anhydrase-2. He discussed the management of osteopetrosis focusing on supportive measures as well as bone marrow transplantation. He concluded by mentioning the role of soluble RANKL inhibitors for the treatment of some forms of osteoclast-poor osteonecrosis.

Skeletal Dysplasias: Experience from the KSA – Dr Maha Faden

Dr Faden discussed the basics of skeletal dysplasia such as definition, history and prevalence of the disease across the globe as well as in the Middle East. She mentioned the absence of any specific age group that gets affected by skeletal dysplasia. The prevalence of skeletal dysplasia is not clear based on the currently available data. It may range from 1/1000 to 4/1000. The most important clinical feature of patients with skeletal dysplasia is short stature. She also discussed radiographic features comparing normal bone with defective bone in skeletal dysplasia. Dr Faden explained various radiological terms used while viewing and opined that clinicians should be aware of these terms while discussing patients with skeletal dysplasia with a radiologist. Dr Faden presented the case of a patient who was short stature and had short hands. She discussed the radiological features of this patient. An interesting case of short stature with hypoplasia of upper extremity and lower extremity was discussed. She pointed out the contrasting radiological features of hypoplasia and pseudohypoplasia. Dr Faden discussed the types, clinical features and radiological differences of OI. The 4 different types of OI have varying dysplasia and reduced bone density. She presented a case of OI and discussed the differential diagnoses of the case. Dr Faden concluded by mentioning that multidisciplinary team work is needed for making the diagnosis of skeletal dysplasia.

Systemic Diseases with Bone Components: Experience from the UAE – Prof Asma Deeb

Prof Deeb began her presentation highlighting the various presentation types of patients having bone-related diseases and how they might present to paediatric endocrinologists. Presentations may range from multiple fractures, bowing of legs, rickets or hypophosphatemic rickets and are short in stature. These patients have abnormal laboratory profile ranging from high or low levels of calcium, high levels of ALP and low levels of Vitamin D. She discussed a case of a female child who presented with humerus fracture as a result of minor trauma, poor growth, irritability, bilateral optic atrophy and abnormal shape of the head. Her parents were second-degree cousins. Paternal cousin of this patient had similar presentation and had died recently. Laboratory investigations of the patient revealed hypocalcemia, high levels of PTH but normal ALP level. Radiographs of the patient showed sclerosis in majority of the long bones that were hollow and associated with radiolucent bands; fracture of the femur and widening of metaphysis. Lateral view of the spine showed osteosclerosis associated with radiolucent bands. The diagnosis was that of osteopetrosis. Due to the fact that the child had multiple anomalies and neurological deficits, bone marrow transplant was not thought to be indicated. She died of respiratory infection few months after diagnosis.

Prof Deeb discussed the clinical features, prognosis, mutations and management of Stüve-Weidmann syndrome by presenting a case. This male child was short in stature and presented with history of repeated chest infections. The patient also had feeding difficulties and recurrent history of pyrexia of unknown origin. Radiographs of this patient showed wide and hollow bones with thick cortices and abnormal metaphyses. Genetic testing confirmed the diagnosis.

Prof Deeb presented the case of a male child who presented with congenital hypothyroidism, multiple congenital anomalies and was short in stature with hearing abnormalities. His parents were first degree cousins. This patient had hairy legs and hyperpigmented symmetrical hairy patches on his back (hypertrichosis). Radiographs of this patient showed diffused expansile osteopenia with osteolysis affecting radius, ulna and metacarpals. Genetic testing showed homozygous mutation in the gene *MMP2* and hence the patient was diagnosed to have H syndrome. This patient had multiple contractures – hand, hip and leg.

In the context of contractures, Prof Deeb also presented the case of a short stature patient with progressive contractures and normal intelligence. Radiographs of this patient showed fragmented head of femur. Genetic testing showed homozygous mutation in the gene *ADAMTSL2*. The child was diagnosed to have geleophysic dysplasia. She also discussed the clinical features of acromesomelic dysplasia.

Prof Deeb discussed various types of presentations among patients with combination of syndromes. She presented a case of a female child who was short in stature and presented with respiratory distress. The child's parents were first-degree cousins. This patient had congenital heart disease (right single atrium), dysplastic teeth with multiple labial frenula, polydactyly and dysplastic nails. Radiographs of this patient showed narrow thoracic cage with shortening of ribs and polydactyly (fusion between 5th and 6th metacarpal bones and soft tissue fusion of 1st and 2nd toes), aplasia of distal phalanges and short pelvis with acetabular roof projections. Prof Deeb presented another case who had similar features – multiple frenula, polydactyly, short stature and dysplastic nails. Radiograph of this patient showed fusion of metacarpal bones as well as metatarsal bones.

The final case in Prof Deeb's presentation was that of a female adolescent who presented with primary amenorrhea. The patient had normal development of secondary sexual characters – breast and pubic hair. The patient was operated for congenital heart disease at the age of 3 years. She had kyphosis and lordosis but short in stature. MRI revealed absence of fallopian tubes, uterus and small cervix. Radiographs revealed fusion at cervical level and lumbosacral level. The patient was diagnosed to have MRKH syndrome.

The conclusion of the speaker's talk was that paediatric endocrinologists come across a multiple category of bone disorders. Majority of endocrine referral is due to presence of short stature among the combination of other features. She highlighted the importance of involving a multidisciplinary teams for management of these disorders.

Summary of Discussion

Discussion was run over managing patients of osteopetrosis with renal tubular acidosis having multiple fractures and how tibial and femoral fractures can be managed by applying external fixation. This way enables the patients to be mobilized earlier and ensures better healing. Applying cast delays healing process as well as mobilization of patients. It was mentioned that fractures in osteopetrotic patients do not heal quickly. The role of growth

hormone in treatment of osteoporosis was discussed. The majority indicated that it does not play a role in treatment of this condition. The role of radiologist expert in skeletal disorder was emphasized.

Closing Remarks

Prof Deeb thanked all the speakers for their input and commented on the immense clinical relevance and educational value of the presentations. She also thanked all the participants for their active participation in the proceedings of the meeting. She acknowledged the interest showed by the members evident from their spirited participation in the discussions and expressed hope that information discussed would be valuable in their daily practice.