ACHONDROPLASIA.EXPERT CONGRESS REVIEWS
EPOS 2021

Welcome to our Achondroplasia.expert congress reviews. Our summaries highlight key data on achondroplasia, skeletal dysplasia, and other disorders of short stature reported at congresses.

Our review of EPOS 2021 includes summaries of many advances in the treatment and management of achondroplasia. Our summaries include new technologies to improve limb lengthening, a complex procedure with a high complication rate and no consensus on its use in achondroplasia, but one that could result in height enhancement in adults with achondroplasia, nonetheless. Claire Shannon showed results from implantable limb lengthening devices in congenital limb length discrepancy, and Emily Dodwell presented data from Sidharthan *et al.* on the use of tantalum beads as landmarks to measure bone growth directly. Finally, Benedick et al. shared data on the use of knee radiographs to predict skeletal maturity, which could be used alongside the new growth charts that are available in achondroplasia.

We also review two symposiums, looking at the natural history of achondroplasia, and the challenges of rare disease diagnosis.

We trust you will find this summary useful in staying current with developments in the field.

The Achondroplasia Team

The abstracts, plenary presentations and symposiums can be found **here**

TECHNOLOGICAL INNOVATION

Technology and smart apps are increasingly becoming part of everyday life, and they can offer utility in the medical setting too.

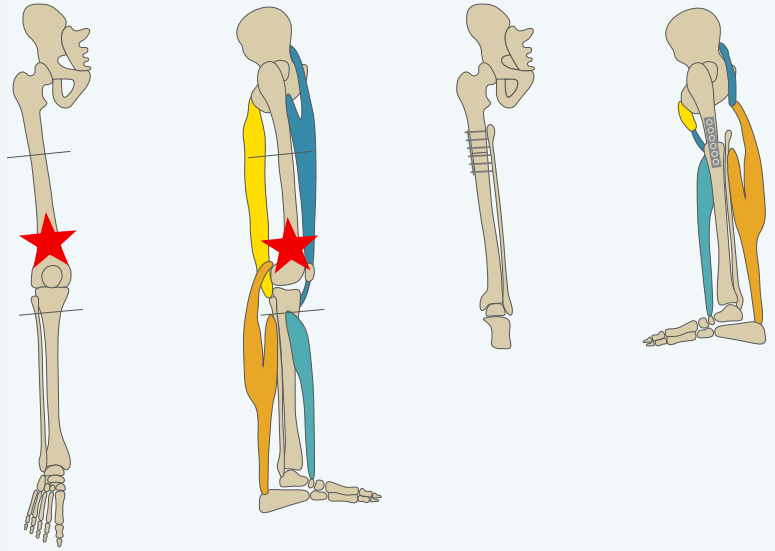
Peter Stevens looked at smartphone monitoring of guided growth, tested in approximately 200 patients over 2 years. Guided growth for angular correction is widespread as a treatment of choice and can be used in growing patients from 18 months to 18 years. Although guided growth is minimally invasive, it consumes time and resources – requiring a clinic visit every 3 months, with full length teleoroentgenogram to document improvement in the mechanical axis. This can be challenging for the patient, their parents, and the surgical clinic team. Stevens suggests a more efficient means of monitoring alignment by examining monthly smartphone photos from caregivers. The images document the child holding a placard and standing with knees (or ankles) touching and are e-mailed to the clinic monthly until the deformities are corrected, whereupon they are instructed to return to the hospital for surgery. Stevens' results show that only a small percentage of parents fail to take and send the pictures as instructed. Only 3 patients experienced overcorrection sufficient to warrant reversal of the 8-plates (medial to lateral), and none required salvage osteotomies. The author concludes that engaging parents in the documentation of progressive improvement of alignment gives them greater investment in the process, and delivers savings in time, travel, and cost – as well as saving unnecessary clinic and imaging time. ▸[OP-015]

SURGICAL ADVANCES

Surgery is an important part of orthopaedic care, and is required for many paediatric joint and bone disorders. New techniques and data were explored for surgical advances in several diseases.

Michiel Van de Sande gave an oral presentation on reconstructions in the very young. He began by discussing bone sarcoma resections, and the challenges of reconstruction for function and growth in young children. About 77.5% of children diagnosed with osteo-sarcoma before the age of 12 survive for 5 years. Generally, it is recommended that limbs should not be lengthened by more than 50% of the final length, with minimal resection for non-invasive growers, and minimal fixation length for stem or motor. The use of radiotherapy before or after surgery may facilitate more marginal resections but cannot always prevent loss of the growth plate.

Winkelman A1 resection



Adapted from de Sande, 2021

Most modern non-invasive growers have comparable survival rates, but implant failures are more common in children under the age of 10, compared to older children. An alternative reconstruction in cases with complications is rotationplasty, where the lower limb is rotated 180 degrees, and the ankle joint – powered by the lower limb muscles – functions as the knee. This is a good choice for young children with joint and physis involvement. Where rotationplasty is not possible, functional limbs can also be reconstructed with 3D implants.

Claire Shannon presented on Extramedullary Implantable Limb Lengthening (EILL) for congenital limb length discrepancy (LLD) as an alternative to external fixation lengthening. This retrospective case review in 23 patients aged 3.5 to 20 years aimed to evaluate whether EILL can extend the indication for implantable limb lengthening to younger and smaller children and replace external fixation as the only method to lengthen children whose medullary canals are too small or whose growth plates would be violated by intramedullary lengthening devices. The patients involved had a variety of diagnoses, including skeletal dysplasia. A small diameter solid rod was inserted in the medullary canal to help maintain alignment and the lengthening nail was affixed outside the bone with screws. Lengthening rate was 0.75mm/day, with daily physical therapy and night extension knee bracing for femurs, ankle dorsiflexion bracing for tibias. Overall, the average lengthening was 48 mm. Complications included one broken

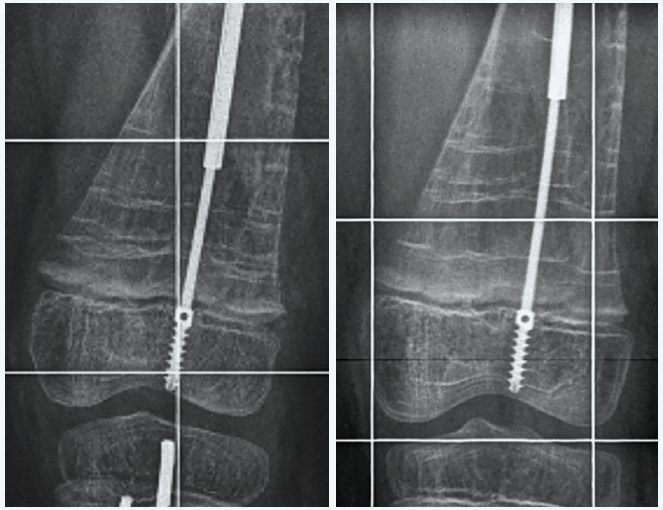
screw requiring revision fixation, and two subluxations of hip treated with open reduction and periacetabular osteotomy. There were no infections and no axial deviation. The authors conclude that EILL is an alternative to external fixation lengthening and extends the indications for implantable lengthening to younger children. However, it is important to follow the same principles as with external fixation lengthening in terms of stabilisation of joints with preparatory surgery and bracing to prevent knee subluxation and contracture. Lengthening should be restricted to 5 cm. ▸ [OP-009]

Emily Dodwell (on behalf of Sidharthan *et al.*) showed that monitoring with tantalum beads demonstrates no clinically significant growth following percutaneous transphyseal screw epiphysiodesis. It has previously been suggested that there is a 6–12-month delay in growth cessation following percutaneous transphyseal screw epiphysiodesis, and the growth inhibition has been estimated based on predicted versus actual growth of the entire bone. Tantalum beads provide landmarks by which growth can be measured directly, and not inferred. This retrospective study aimed to evaluate growth at the physis following percutaneous transphyseal screw epiphysiodesis (PETS) using tantalum bead markers inserted medially and laterally both proximal and distal to the physis. Inter-bead distance perpendicular to the physis was measured on calibrated radiographs.
The study included 18 patients (12 boys and 6 girls) with predicted LLD> 2 cm at maturity who underwent PETS of the distal femur and/or proximal tibia with tantalum bead placement and had at least 6 months' post-operative imaging. Median bone age was 12.5 and 13.3 years among girls and boys, respectively. Median current LLD was 1.4 cm and median predicted LLD at time of skeletal maturity was 2.7 cm. Median follow-up was 53 weeks.

In both the femoral and tibial physes, median change in inter-bead distance was 0 mm. The authors concluded that PETS demonstrated immediate cessation of growth in all patients. This technique inhibits growth at the physis effectively, with no evidence of time lag in growth inhibition. No complications related to transphyseal screws or the tantalum beads were identified. ▸ [OP-074]

A poster from Popkov *et al.* discussed the use of titanium telescopic rodding and reduced external fixation in paediatric osteogenesis imperfecta (OI) patients. The major limitation of any intramedullary telescopic system is rotational and longitudinal instability. This study aimed to examine the outcomes of deformity correction by combined technique uniting titanium telescopic rod and reduced Ilizarov frame in 12 children with OI with a minimum follow-up of 1 year. In 5 cases, telescopic rod insertion was performed simultaneously with Ilizarov frame removal from the segment previously operated; in other consecutive surgeries, there was a 2–6-month interval between operations. Telescoping gain related to spontaneous growth assessed at 1 year was 15.9 ± 2.3 and 13.7 ± 3.1 mm in the femur and tibia, respectively. The authors concluded that – despite the abnormal bone – a combination of titanium telescopic rod with reduced external fixation provides advantages in orthopaedic surgery for children with OI. Titanium alloy telescopic rod is not prone to

Telescopic rodding of tibia: amount of telescoping since frame removal = 19 mm



Popkov *et al.* [EP-004]

limited telescoping, deformity relapse, or rod migration. Children demonstrated walking with weight-bearing early in the post-operative period. Temporary gait changes were influenced by the size of the external device, and by strategies to reduce pain at the pin sites. ▸ [EP-004]

The surgical treatment of severe cervical kyphosis in diastrophic dysplasia was covered in a poster from Heydemann *et al.* The incidence of cervical kyphosis is 15–44% in children with diastrophic dysplasia. Although spontaneous improvement is seen in 75%, progression can result in severe deformity, spinal cord compression, and neurologic injury. Bracing can delay surgery, but treatment requires spinal fusion, sometimes in combination with spinal cord decompression. This single-centre retrospective series included 47 patients with diastrophic dysplasia treated from 1984–2017 with minimum 2-year follow-up. Patients underwent posterior fusion plus anterior corpectomy, decompression and fusion for spinal cord compression. Cervical kyphosis was found in 27 of the patients – an incidence of 57%, which is higher than previously reported. Of these, 21 patients spontaneously improved, but 6 required surgery. The results demonstrated substantial improvement in deformity and sagittal balance, with 100% fusion rate and no major adverse events or neurologic injuries. Given the high incidence reported, the authors concluded there is a need for vigilance. In children with diastrophic dysplasia, surgical correction of severe cervical kyphosis can be achieved safely and reliably. ▸ [EP-005]

BASIC SCIENCE

The basic science session included a round-up of presentations looking at animal models and imaging considerations in orthopaedics.

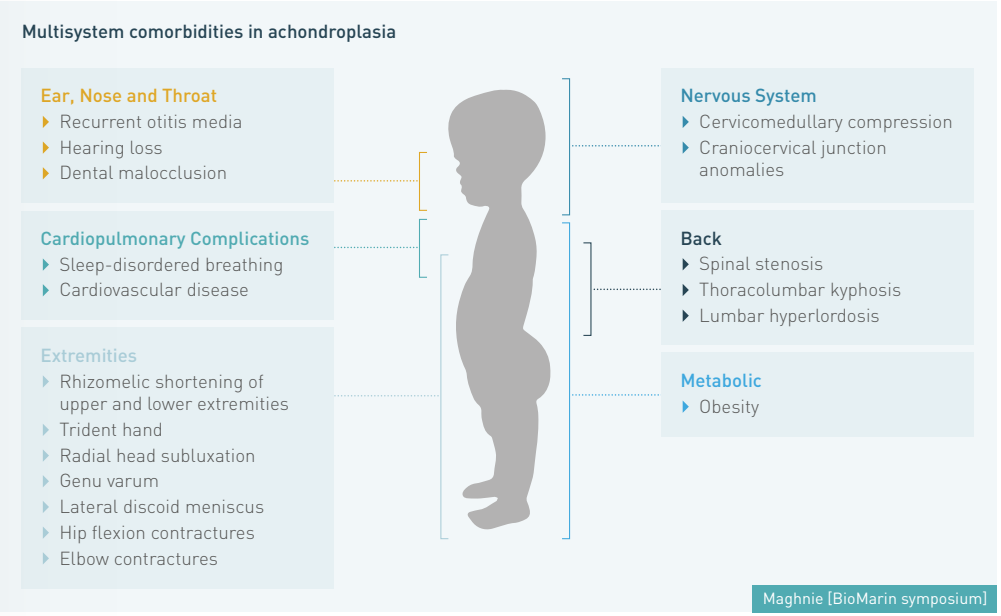
Raymond Liu (on behalf of Benedick *et al.*) described using knee radiographs during pre-adolescence to estimate skeletal maturity. Knowing skeletal age is useful in the treatment of LLD; however, a quick, accurate method in this age range is lacking. The authors analysed serial knee radiographs leading up to the chronological age associated with 90% of final height (an enhanced skeletal maturity gold standard compared to peak height velocity) in 75 children. The goal was to develop a quick, accurate and reproducible knee skeletal maturity system that would outperform current methods in the pre-adolescent age range. Epi- and metaphyseal widths of the distal femur, proximal tibia, and proximal fibula were measured, and the ratio calculated. Greulich and Pyle (GP) bone ages were assigned using radiographs of the left hand. In total, 258 left knee radiographs from 39 girls (mean age 8.6) and 36 boys (mean age 10.6) were included. The results showed a strong positive correlation between the epiphyseal: metaphyseal ratio value and years away from reaching 90% of final height, with Pearson R values of 0.80, 0.84, and 0.84 for the femur, tibia, and fibula, respectively (all $P<0.001$). When split by sex, the results for females were more consistent than those for the males. Similar findings were found for the femur, tibia and fibula. Regression analysis showed high correlation in predicting years away from 90% of final height using the ratios and demographics, which was superior to demographics alone, and comparable to GP and demographics. The authors concluded that skeletal maturity can be predicted with a high degree of accuracy during pre-adolescence at a level comparable to GP using three simple knee radiograph parameters. This method would allow skeletal maturity assessment in children with LLD without a separate hand radiograph. ▸[OP-089]

Marjolein Caron evaluated impaired skeletal development in skeletal immature mice by antirheumatic agents. Impairment of physical growth is a known problem in children with juvenile idiopathic arthritis (JIA), with 39% of children experiencing restricted growth. This impairment is often explained by sustained inflammation; however, the effect of treatment for JIA on skeletal growth is not known. In this animal model, skeletally immature mice were treated for 10 weeks with daily naproxen or placebo, and methotrexate (MTX) or placebo 3 times a week. Growth plate characteristics, longitudinal bone growth, and bone micro-architecture were analysed at 15 weeks, showing that tibia and femur length was significantly reduced in the naproxen- and MTX-treated mice. Growth plate analysis of the tibia revealed a significantly thicker proliferative zone, with a higher intensity of Safranin O and Collagen type II staining in both experimental groups. The hypertrophic zone of the MTX- and naproxen-treated mice was thinner than their controls, which was accompanied by a lower Collagen type X staining. Analysis of the subchondral bone showed significant alterations in bone volume and trabecular structures in both the MTX- and naproxen-treated mice. To further elucidate a potential biomolecular mechanism explaining these results, endochondral ossification was mimicked *in vitro*, showing significant deregulation of genes in the PTHrP/Ihh pathway. The authors concluded that naproxen and MTX have a profound effect on endochondral ossification during growth plate development, with increased expression of chondrocyte markers and decreased hypertrophic markers, resulting in aberrant subchondral bone morphology and reduced bone length. ▸[OP-091]

ACHONDROPLASIA NATURAL HISTORY

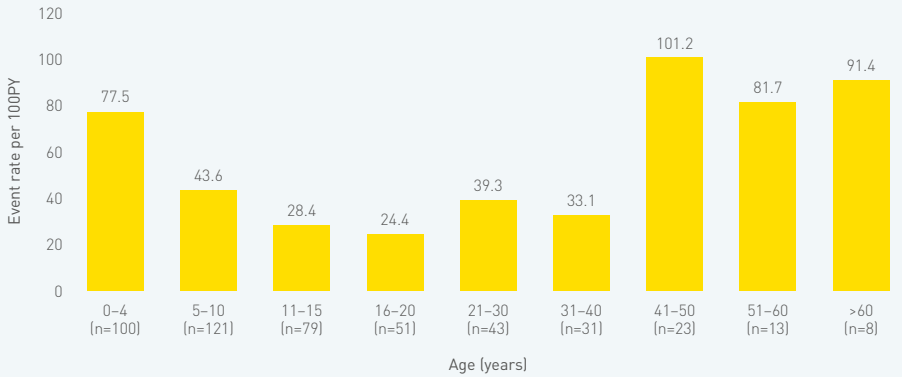
A BioMarin-sponsored symposium looked at the natural history and current management of achondroplasia. The symposium was chaired by João Cabral, with presentations from Mohamad Maghnie, Encarna Guillén-Navarro, and Antonio Leiva-Gea.

Professor Maghnie began with a talk on the genetic causes and natural history of achondroplasia.We know that many organ systems are involved in achondroplasia, affecting people at different ages. Professor Maghnie looked at real-world data from the



Maghnie [BioMarin symposium]

LIAISE: Burden of medical conditions and disorders*



*Medical conditions and disorders are those that required a visit to the doctor.

Maghnie [BioMarin symposium]

LIAISE study – a multinational, observational natural history study being conducted across Europe to examine the lifetime impact of achondroplasia. This initiative aims to quantify the impact across the age spectrum by measuring the clinical burden, healthcare resource use, and health-related quality of life. Data are being collected from 13 sites in six countries. Initial results show a bimodal U-shaped distribution of medical events by age group, with youngest and oldest the most affected. ENT and neurological issues are more common children, with pain, ENT issues (excluding otitis media) and spinal issues increasing with patient age. The most frequently reported complication by system organ class is musculoskeletal and connective tissue disorders, and nervous systems issues – each reported in up to 60%.

Professor Maghnie concluded by stating that many unmet needs remain for people with achondroplasia. These are physical, psychosocial, economic, and environmental –some of which can be avoided if they are detected early. There are also still gaps in knowledge, notably around potential complications and functional consequences across the lifespan, and the impact of emerging disease-modifying therapies.

Professor Guillén-Navarro looked at the current care pathway for people with achondroplasia. For efficient clinical management, it is critical to understand the natural history – but in general there is a scarcity of clinical practice guidelines to assist appropriate decision making. With advances in potential drug management for achondroplasia, there is a need to better understand the natural history and clinical care framework. Recently, an expert meeting was convened to address this issue in Europe, beginning with an analysis of the healthcare set-up, guidelines, and patient associations in five countries. There are significant differences in how achondroplasia is managed, and – to date – France is the only country with national guidelines. Patient organisations in all countries provide support and collaborate in the care pathway. In all five countries, pre-natal diagnosis is considered preferable, and molecular diagnosis is the gold standard. In infancy and early childhood there is a typically follow-up every 3–6 months, with care given by a multidisciplinary team. There are also yearly follow ups at specialist centres, in which the key areas monitored are weight, dental issues, and leg deformities. There is evidence that limb-lengthening is common in Italy and Spain, but rarely undertaken in France, Germany, and the UK. Notably, a gap has been identified for the transition into adult care, with limited structured care. Adults have specific needs, such as pain, obstetric advice, genetic counselling, and support in the workplace. With potential new therapies on the horizon, more systematic and structures

Healthcare set-up for achondroplasia

Centralised	Decentralised
France ▸ National network for skeletal dysplasia consisting of one national coordinating Centre of Reference (Necker in Paris) ▸ 21 Centres of Competence in the regions; and two Centres of Reference for adults (in Paris) ▸ Expert centres belong to the bigger network 'Filiere OSCAR'	**Germany** ▸ Approx 35 centres for rare diseases, with some (5–7) of these specialised in bone diseases ▸ Decentralised healthcare system ▸ Care of ACH patients may be organised by paediatric orthopaedic, clinical genetics or paediatric endocrinology departments depending on region
UK ▸ UK-wide ACH network has been established to develop consistent approaches in managing the patient journey to the specialist centres	**Italy** ▸ Every region has one or more rare disease centres and a centre of expertise ▸ Only few institutions specialised (multidisciplinary) in treatment of ACH patients ▸ This does allow some centralisation of care ▸ Devolved care in many regions
	Spain ▸ 17 regional health system with autonomous decisions ▸ Each region responsible for implementing follow-up care for patients ▸ a few reference centres for surgical treatments of skeletal dysplasia ▸ Clinical genetics is not yet recognised as a speciality in Spain but experts trained abroad providing service and raising profile

Guillén-Navarro [BioMarin symposium]

care is needed for standardisation of care and access to specialist services, and guidelines are need for the different aspects of care.

Dr Leiva-Gea focused on current thinking on limb lengthening in people with achondroplasia. Limb lengthening is not typically part of the natural history, and there is no consensus on its use at present. If limb length can be shown to have an impact on health-related quality of life then lengthening surgery may have important role to play, but at present it is not clear which aspects of achondroplasia impact quality of life. There is some evidence suggesting upper limb lengthening provides functional improvement and gains in quality of life, including self-esteem. Leiva-Gea and colleagues have recently published a protocol on limb lengthening, showing different steps – maintaining the idea that some people with achondroplasia will benefit from limb lengthening. Limb lengthening increases overall height and arm span, and improves proportionality. But the true impact on functionality, quality of life, and metabolic issues is not known, and more studies are needed to create more robust evidence on the efficacy and safety, and to identify which patients are appropriate for this intervention.

CHALLENGES OF RARE DISEASE DIAGNOSIS

The Ipsen symposium focused on the challenges of rare disease diagnosis, centred around a series of patient cases. The session was chaired by Peter Kannu, who also gave a presentation, alongside Vladimir Kenis.

Dr Kannu highlighted that while a rare disease is defined as one with an incidence of fewer than 5 cases per 10,000 population the vast majority are far less common than this. Although individually rare, collectively rare diseases have a significant burden, and 1 in 17 people are affected by a rare disease at some point in their life. Typically, diagnosis can take a long time, which causes deterioration in health, lack of treatment, and potential harm and costs.

Heterotopic ossification is a rare disease that causes pathological formation of extra-skeletal bone in muscles and soft tissue. Dr Kenis discussed two children with deformities of the foot. On referral to genetic testing, diagnosis was confirmed as fibrodysplasia ossificans progressiva (FOP) – a type of heterotopic ossification with a prevalence of 1.36 per million individuals that exists across a spectrum of presentations. To date, there is no conventional treatment strategy for heterotopic ossification, and surgery can be ineffective and dangerous, leading to further deterioration. Dr Kenis stressed that orthopaedists are often the first specialty consulted, and it is important to be able to identify rare diseases. He concluded that genetic testing is the easiest way to confirm a rare disease, and to find the most appropriate treatment.

FOP is an incredibly rare condition caused by a spontaneous missense mutation in ALK2/ACVR1. Genetic testing is key to FOP diagnosis. Dr Kannu presented a case of a 2-year-old boy, which was subsequently confirmed as FOP. Aggressive juvenile fibromatosis is a common misdiagnosis for FOP, and early lesions can look identical under the microscope. Other differential diagnoses include autosomal dominant progressive osseous heteroplasia, osteoma cutis, and Albright's hereditary osteodystrophy.

LIST OF ABBREVIATIONS

EILL	Extramedullary Implantable Limb Lengthening
FOP	Fibrodysplasia Ossificans Progressiva
GP	Greulich and Pyle
JIA	Juvenile Idiopathic Arthritis
LLD	Limb length discrepancy
MTX	Methotrexate
OI	Osteogenesis Imperfecta
PETS	Percutaneous Transphyseal Screw Epiphysiodesis

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