

ABSTRACT BOOK

Congress OI in 2016

Latest Developments in Osteogenesis Imperfecta



6th - 8th October 2016 Lisbon

apoi
associação portuguesa de
osteogénese imperfeita

FUNDACIÓN
AHUCE
Osteogénesis imperfecta

Table of Contents

| | |
|--|----|
| Conference Program..... | 6 |
| Abstract Key Speakers..... | 9 |
| Oral Communications..... | 24 |
| Abstracts Posters Sessions..... | 33 |
| Pre-Congress Course..... | 70 |
| Bios Speakers, Authors and Moderators..... | 75 |

Congress
01 *in* 2016

Direct Links

- [Scientific and Organizing Committee](#)
- [Conference Program](#)
- [Abstracts Key Speakers](#)
 - [Prof Francis Glorieux. Diagnostic Approaches for OI](#)
 - [Dr Belén Sagastizábal. Osteogenesis imperfecta in children: An extensive institutional experience](#)
 - [Dr Amaka Offiah. Imaging in OI - What is New?](#)
 - [Dr Elena Sevillano. Ocular manifestations in Osteogenesis Imperfecta](#)
 - [Dr M. Joaquín de Nova García. Oral findings in children with osteogenesis imperfecta. Dental implications of treatment with bisphosphonates](#)
 - [Dr Ricardo Sanz. Osteogenesis Imperfecta and hearing loss. The new Approach after biphosphonates](#)
 - [Luisa Barros, Margarida Custódio dos Santos and Ana Filipa Pires. PainLess - the Youngest Take Control!](#)
 - [Dr Markus Bastir. 3D Morphometrics of Breathing Kinematics and its Potential Implications for Respiratory Issues in OI](#)
 - [Dr Clara I. Rodríguez. Stem-Cells: Application to the Treatment of Osteogenesis Imperfecta](#)
 - [Ms Ingunn Westerheim. European Reference Networks - the patient organization's perspective](#)
 - [Prof Nicholas Bishop. European Reference Networks - the professional's perspective](#)
 - [Ms. María Barbero. International Cooperation in Osteogenesis Imperfecta: The OI Patient-Network](#)
 - [Dr Suken A. Shah. Management of Spinal Conditions in Osteogenesis Imperfecta](#)
 - [Dr Ana Bueno Sánchez. New Techniques in Orthopaedic Surgery](#)
 - [Pht Miguel Rodriguez Molina. Physiotherapy Concepts in Osteogenesis Imperfecta](#)
 - [Prof Francis Glorieux. New Pharmaceutical Treatments](#)
- [Oral Communications](#)
 - [Surgical treatment of Osteogenesis Imperfecta in a Developing Country with Resource Limitation: Results of Rodding and Impact on Ambulation and Refracture](#)



- [The best surgical technique in the treatment of the Hip in OI](#)
- [Growth cartilage injury in surgery of the femur and tibia in OI](#)
- [Quantitative ultrasound \(QUS\) and Dual X- ray absorptiometry \(DXA\) in patients affected by Osteogenesis imperfecta](#)
- [Renal ultrasound screening for nephrocalcinosis in children with osteogenesis imperfecta](#)
- [Treatment with neridronate in adults and children with Osteogenesis Imperfecta: Data from Open-label, not controlled, three-year italian study](#)
- [Sternal geometry, ventilatory and thoraco-abdominal pattern in children with Osteogenesis Imperfecta](#)

- [Abstracts Poster Sessions](#)

- [Rare Commons: an online platform to facilitate clinical research in Osteogenesis Imperfecta](#)
- [Somatic COL1A1 mosaicism in a newborn with Osteogenesis Imperfecta](#)
- [Osteogenesis imperfecta in one gemellus from the twin-pregnancy after in vitro fertilisation](#)
- [Sensory Integration Dysfunction in Osteogenesis Imperfecta: A Case Study](#)
- [Bruck Syndrome in a Mozambican patient with a homozygous mutation in FKBP10 gene](#)
- [Osteopathic Manipulative Treatment Effects on Bone Mineral Density and Quality of Life in OI Adults treated with Neridronate](#)
- [Is participation in children with type 1 OI influenced by wearing a DEFO?](#)
- [Development of innovative orthopedic braces for the care and rehabilitation in osteogenesis imperfecta and skeletal dysplasias](#)
- [Online self-help groups for osteogenesis imperfecta patients and their families](#)
- [The London Osteogenesis Imperfecta Team: Offering Highly Specialised Tertiary Care across the South East of England](#)
- [Osteogenesis Imperfecta in Honduras. Advances](#)
- [Psychological aspects of OI](#)
- [Evaluation of outreach visits to new born babies with osteogenesis imperfecta](#)
- [Osteogenesis imperfecta in children evaluated in the Pediatrics Department: case review](#)
- [It is a family stressful experience: Pain in children with Osteogenesis Imperfecta](#)
- [Osteogenesis Imperfecta: The experience of one single center in Lisbon](#)
- [Clinical Characterization of a Group of Portuguese Patients with Osteogenesis Imperfecta: a First Report](#)



- [Abstracts Pre-Congress Course](#)
 - [Introduction to Osteogenesis Imperfecta](#)
 - [Classification and Genetic Diagnosis](#)
 - [The Impact of Diagnoses on Families](#)
 - [Medical Treatments in Osteogenesis Imperfecta](#)
 - [Surgical Treatments in Osteogenesis Imperfecta](#)
 - [Clinical Case Studies](#)

- [Bios Speakers, Authors and Moderators](#)

Scientific Committee

- Dr Ana M. Bueno Sánchez
- Dr Manuel Cassiano Neves
- Prof Margarida Custódio dos Santos
- Prof Joaquín de Nova
- Dr Patrícia Dias
- Prof Francis Glorieux
- Dr Fátima Godinho
- Dr Pilar Gutiérrez
- Dr José Ignacio Parra
- Dr Belén Sagastizabal Cardelus

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- Mrs María Barbero
- Mrs Carminda Barreiros
- Mrs Céu Barreiros
- Mrs Fátima Godinho
- Mrs Julia Piniella
- Mrs Isabel Rufo



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Conference Program

October 6th

PreCongress Course - *OI Basics*

(the sessions of this course will be spoken in Portuguese)

12h00 – Registration

14h00 – **Welcome and reception**

Dr Fátima Godinho

14h30 – **Introduction to Osteogenesis Imperfecta**

Dr Anabela Bandeira

15h00 – **Classification and Genetic Diagnosis**

Dr Patricia Almeida Dias

15h30 – **The Impact of Diagnoses on Families**

Prof Margarida Custódio dos Santos

16h00 - Coffee break

16h30 – **Medical Treatments of OI**

Dr Paula Garcia

17h00 – **Surgical Treatments of OI**

Dr João Campagnolo

17h30 – **Clinical Case Studies**

Dr Fátima Godinho

October 7th

09h00 - Session I - **powered by APOI:**

Diagnostic Approaches and Pharmacological Therapy

Moderator - Dr Paula Garcia

Diagnostic Approaches for OI

Prof Francis Glorieux

Osteogenesis imperfecta in children: An extensive institutional experience

Dr Belén Sagastizábal

Imaging in OI - What is New?

Dr Amaka Offiah

10H30 - Coffee break and Poster Session (Group 1)

11h00 - Session II - **powered by OIF:**

Beyond fractures

Moderator - Dr Fátima Godinho

Ocular Impact in Osteogenesis Imperfecta

Dr Elena Sevillano

Oral findings in children with osteogenesis imperfecta. Dental implications of treatment with bisphosphonates

Dr M. Joaquín de Nova García (with simultaneous translation)

Osteogenesis Imperfecta and hearing loss. The new Approach after biphosphonates

Dr Ricardo Sanz



12h30 - Opening Ceremony

Ministry of the Portuguese Health Department: Dr Fernando Regateiro
President of Faculdade de Medicina de Lisboa (to be confirmed)
President of Fundación AHUCE: Mr Gerardo Muñoz Fernández
President of APOI: Mrs M. Céu Barreiros

13h00 – lunch

**14h30 - Session III - powered by Care4BB Foundation:
New Projects and Developments in Osteogenesis Imperfecta**

Moderator - Dr Patrícia Dias

PainLess - the Youngest Take Control

Prof Luísa Barros

3D Morphometrics of Breathing Kinematics and its Potential Implications for Respiratory Issues in OI

Dr Markus Bastir

Stem-Cells: Application to the Treatment of Osteogenesis Imperfecta

Dr Clara I. Rodriguez

15h30 - Coffee break and Poster session (Group 2)

16h00 - Session IV - powered by OIFE:

International Networks and Cooperation in Osteogenesis Imperfecta

Moderator - Ms Ute Wallentin

European Reference Networks - the Patient Organization's perspective

Ms Ingunn Westerheim

European Reference Networks - the Professionals' Perspective

Prof Nicholas Bishop

International Cooperation in Osteogenesis Imperfecta: The OI Patient-Network

Mrs María Barbero

17h00 - Free Communications and posters

Moderator – Dr Cassiano

Bhaskar, Atul

Surgical treatment of Osteogenesis Imperfecta in a Developing Country with Resource Limitation: Results of Rodding and Impact on Ambulation and Refracture

Bueno, Ana

The best surgical technique in the treatment of the Hip in OI

Bueno, Ana

Growth cartilage injury in surgery of the femur and tibia in OI

Celli, Mauro

Quantitative ultrasound (QUS) and Dual X-ray absorptiometry (DXA) in patients affected by Osteogenesis imperfecta

Crowe, Belinda

Renal ultrasound screening for nephrocalcinosis in children with osteogenesis imperfecta

Fassio, Angelo

Treatment with neridronate in adults and children with Osteogenesis Imperfecta: Data from Open-label, not controlled, three-year italian study

Lo Mauro, Antonella

Sternal geometry, ventilatory and thoraco-abdominal pattern in children with Osteogenesis Imperfecta



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October 8th

09h00 - Session V - powered by Fundación AHUCE:

Orthopaedic Surgery, Physical Therapy and other Challenges

Moderator - Dr Carolina Escalda

Management of Spinal Conditions in Osteogenesis Imperfecta

Dr Suken A. Shah

New Techniques in Orthopaedic Surgery

Dr Ana Bueno Sanchez (with simultaneous translation)

Physiotherapy Concepts in Osteogenesis Imperfecta

Pht Miguel Rodriguez Molina

10h30 - Coffee break and Poster session (Group 3)

11h00 - Honorary Lecture

Moderator - Dr Manuel Cassiano Neves

New Pharmaceutical Treatments

Prof Francis Glorieux

12h00 - Closing Session

On Behalf of the Scientific Committee of APOI:

Dr Manuel Cassiano Neves

On Behalf of the Scientific Committee of Fundación AHUCE:

Dra Ana Bueno Sánchez



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Abstracts Key Speakers

October 7th

09h00 - Session I - *powered by APOI*:

Diagnostic Approaches and Pharmacological Therapy

Moderator - **Dr Paula Garcia**

Prof Francis Glorieux

Diagnostic Approaches for OI

Osteogenesis Imperfecta (OI) is a heritable disorder characterized by bone fragility caused by alterations in bone quantity and quality. The term OI has been used to describe the clinical features of the disorder since the nineteenth century long before any underlying mutations were described. The spectrum of severity is wide and justified the classic Sillence classification (I-IV). There are however variations within each class. Thus it is more realistic to use severity as the central parameter and define mild, moderate, severe and lethal forms of OI. Besides skeletal manifestations (limb deformities, scoliosis, wormian bones, short stature), other organs' involvement include blue sclera, dentogenesis imperfecta, joint laxity, early bruising, muscle hypotonia, hearing loss and various neurological complications including basilar invagination. Comprehensive radiological skeletal survey and assessment of bone mineral density by DXA are standard procedures. Biochemical evaluation of bone and mineral metabolism will include analysis of biomarkers to assess bone formation and resorption. Molecular diagnosis by DNA sequence analysis will be useful to delineate the exact cause of OI and identify affected family members with great accuracy. In specific circumstances, analyses of iliac crest bone biopsies (undecalcified specimens) will help in the diagnosis of rare forms of OI

Dr Belén Sagastizábal

Osteogenesis Imperfecta in Children: An Extensive Institutional Experience

Osteogenesis imperfecta is a clinically heterogeneous heritable connective tissue disease caused by mutations impairing collagen type I. It is characterized by a reduced amount of bone mass with recurrent fractures due to minimal trauma and bowing deformities of the long bones as the principal signs in severe forms. Non-skeletal manifestations as dentinogenesis imperfecta (DI), blueish/greish discoloration of the sclera, hearing loss and a decrease in pulmonary function could be found. Almost 90%

9



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are caused by heterozygous mutations in COL1A1 and COL1A2 genes encoding the two collagen type I alpha chains causing qualitative and quantitative abnormalities. In the last few years more than thirteen genes have been identified in patients with an OI phenotype involving folding and post-translational modifications of the collagen, and more recently bone mineralization and osteoblast differentiation. This has made a breakthrough in the knowledge of this disease and an extension of the therapeutic options.

The use of cyclic intravenous therapy with Biphosphonates in children with OI has meant a change in the natural history of this disease. Since the implementation in our center of the first protocol of treatment with cyclic pamidronate in the year 2000 more than 1200 cycles of pamidronate and 400 of zoledronic acid have been administered in more than 90 children from all ages, decreasing the pain and the number of fractures by increasing bone mass. Recently new antiresorptive drugs like Denosumab become available, allowing its use in patients with OI type VI with a favorable initial response.

Despite the progress made in the medical treatment in recent years, certain concerns about the long-term effects of these drugs in patients who began treatment in their first years of life continue to exist. Further studies are needed to optimize Biphosphonate regimens and to investigate new antiresorptive and osteoanabolic treatments for these children.

Dr Amaka Offiah

Imaging in OI - What is New?

Baseline imaging when a child is suspected to have OI consists of a modified skeletal dysplasia skeletal survey. This should include Townes and lateral skull, lateral thoracolumbar spine, AP pelvis, AP chest, AP one upper limb, AP one lower limb and DP left hand and wrist. The protocol is modified to include a Towne's view of the skull which is superior to standard AP skull for identifying Wormian bones. In addition to reduced bone density and Wormian bones, radiographic features in support of OI include multiple long bone, rib and vertebral compression fractures, slender ribs and long bones, bowing of the long bones, skull vault abnormalities (platybasia, Tam O'Shanter deformity, basilar invagination, basilar impression), popcorn calcification and features specific to certain types of OI e.g. radial head dislocation, hyperplastic callus and interosseous membrane calcification (type V) or rhizomelia (type VII).

A completely normal skeletal survey does not exclude a diagnosis of OI and despite certain drawbacks of the technique, particularly in children, dual energy x-ray absorptiometry (DXA) is the current gold standard for assessment of bone density. While ultrasound and magnetic resonance-based methods of bone density assessment exist, other than DXA, the most clinically established (certainly in adults) are quantitative (peripheral) computed tomography



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(QCT/pQCT) performed using standard CT machines and high resolution peripheral computed tomography (HRpQCT). The latter, being a low dose technique has potential for use in children.

Once the diagnosis of OI has been established, routine surveillance imaging includes 6-monthly DXA and 6-monthly or annual lateral spine radiographs). The need for and frequency of lateral basal skull radiographs is not well established and we are currently assessing the various radiographic measurement parameters (basal angle, McGregor's line, McRae's line) and comparing them to magnetic resonance imaging (MRI). In another study, we have shown that horizontal beam lateral (whether radiographs or CT scout views) are of better image quality (less obliquity) than standard lateral skull radiographs for skull base measurements.

Radiographs of other skeletal sites are obtained on the basis of clinical need, however routine lateral spine imaging is important because vertebral compression fractures are often clinically silent and their presence may prompt initiation of bisphosphonate therapy in order to prevent further fractures and abnormalities/complications of spinal curvature.

The diagnosis of vertebral fractures from lateral spine DXA (termed "VFA" – vertebral fracture assessment) is standard in adults. We have recently shown VFA in children to be cost-effective and as accurate and reliable as but with considerably less radiation dose penalty than vertebral fracture diagnosis from radiographs; we therefore propose that VFA should now also be routine in children. However, given the generally poor reliability of vertebral fracture diagnosis from either radiographs or DXA, a clear definition of normal vertebral morphometry in children is required, a process that will be aided by the optimization of existing/development of new semi-automatic software programs.

The presentation will cover all of the above, showing example images and highlighting the pros and cons of established and newer modalities/techniques as appropriate.

11h00 - Session II - *powered by OIF:*

Beyond fractures

Moderator - **Dr Fátima Godinho**

Dr Elena Sevillano

Ocular Manifestations in Osteogenesis Imperfecta

There is significant clinical variability in ocular manifestations within one single type of Osteogenesis imperfecta, and even within one single family. Most of these abnormalities are associated with anterior segment and ocular surface anomalies. Some of the most frequent manifestations are: Blue sclerae and Saturn's rings are the main manifestations on the sclera. On the cornea and the lens, megalocornea, keratoconus, zonular cataract and lens subluxation are the main abnormalities.



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As for the eyeball posterior segment, primary optic atrophy or secondary optic atrophy resulting from chronic papilledema, glaucoma and vitreous and retinal haemorrhages are frequent manifestations.

Amongst these clinical signs, blue sclera is the most frequent abnormality associated with Osteogenesis imperfecta, which can appear in up to 70% of all Osteogenesis imperfecta patients. According to the Silience classification, blue sclerae usually occur in types I and II on an on-going basis, while it tends to fade away in types III and IV as the patient becomes adult. The blue colour is caused by scleral thinning, which allows the uveal pigment to show through the thinned tissue.

Another highly frequent manifestation of *OI* is Keratoconus. Keratoconus is a degenerative disorder of the eye in which the cornea acquires a conical shape as a result of corneal thinning and protrusion, which causes an increase in the curvature of the cornea and presents with myopia and irregular astigmatism. It tends to present bilaterally, although asymmetrically. The main way to prevent it is by avoiding eye rubbing.

Although irregularly and with undetermined frequency, cases of hyperopia, progressive myopia with posterior staphyloma, spontaneous detachment of Descemet's membrane and glaucoma have been reported.

To sum up, all patients with osteogenesis imperfecta who present any ocular abnormalities must be informed that there is no cure for blue sclerae and they should be advised to wear safety protective glasses for prevention purposes, since these patients are more vulnerable to injuries. They should also be advised to avoid eye rubbing and to use sunglasses in cases of severe photophobia, prescription glasses or contact lenses in cases of refractive defects and to attend an annual eye exam since age 6, even when there are no associated ocular symptoms, as well as in the event of an eye injury.

Dr M. Joaquín de Nova García

Oral Findings in Children with Osteogenesis Imperfecta. Dental Implications of Treatment with Bisphosphonates

Sin duda, cuando abordamos los intereses, las preocupaciones y los objetivos de las investigaciones más actuales, relacionados con las repercusiones orales de la Osteogénesis Imperfecta (*OI*) nos encontramos que están más vinculados a los tratamientos que reciben los pacientes, que a las propias características orales y craneofaciales asociadas a la enfermedad.

Desde que a finales de la década de los 80' (Devogelaer JP et al, 1987) se dieron los primeros pasos en la incorporación de los bifosfonatos al tratamiento de la enfermedad, actualmente los protocolos en base a estos medicamentos se han consolidado como uno de los pilares terapéuticos de la enfermedad. A medida que se han ido conociendo sus mecanismos de acción en células y tejidos diana, los clínicos hemos comprendido mejor el alcance de sus efectos sistémicos y su potencial implicación en diferentes



procesos fisiológicos. Las diferentes estructuras que conforman el macizo craneofacial no sólo no han permanecido ajenas a estos efectos, por diferentes motivos han sido el centro de atención de algunos de sus efectos secundarios, de los que constituyen un área de investigación muy actual. Los protocolos terapéuticos actuales de la OI, al incorporar fármacos más potentes de 3^a generación (ac. zoledrónico) deben alertarnos para anticipar potenciales efectos más deletéreos.

Partiendo de las características orales y craneofaciales asociadas a la propia enfermedad (dentinogénesis imperfecta, maloclusión, desarrollo craneofacial alterado), llevamos a cabo una revisión con aportaciones personales acerca de los potenciales efectos que el tratamiento con bifosfonatos puede desencadenar en los procesos fisiológicos de desarrollo de las estructuras craneofacial y dental, así como en las terapias aplicadas (tratamiento de ortodoncia).

Desarrollo craneofacial. En relación con el desarrollo craneofacial, algunos trabajos de investigación (Waltimo-Sirén J et al, Jensen BL et al, Chang P et al) han aportado luz sobre los efectos de la OI en el crecimiento de los huesos craneofaciales, lo que ha permitido definir un fenotipo muy característico en las formas más graves de la enfermedad y orientar el tratamiento correctivo de la maloclusión dental concomitante. Estudios que han contemplado el efecto de la propia enfermedad sobre el desarrollo craneofacial, aún son escasos los centrados en los potenciales efectos de los bifosfonatos sobre el remodelado esquelético craneofacial. Recientemente estudios de experimentación animal (Lézot F et al, 2014) describen los potenciales efectos de los bifosfonatos de 3^a generación a altas dosis sobre la formación craneofacial en ratas en desarrollo y alertan de su extrapolación en niños.

Desarrollo dental y erupción. Los tejidos duros del diente son los más mineralizados del organismo. Su alta riqueza en cristales de hidroxiapatita constituye un atractivo poderoso al depósito e interacción con los bifosfonatos circulantes en los organismos en desarrollo. Sus efectos inhibitorios sobre la mineralización de esmalte y dentina han sido plenamente confirmados en experimentación animal (ratas) y sobre todo con bifosfonatos no nitrogenados (etidronato). Las alteraciones observadas pueden ser el resultado del efecto físico-químico sobre la mineralización, sin descartar los posibles efectos celulares directos en las células implicadas en el proceso (ameloblastos, odontoblastos). Se han llevado a cabo intentos recientes por confirmar estos hallazgos en humanos sin incluir el colectivo de personas con OI.

También el proceso fisiológico de la erupción dental se podría ver interferido por el efecto antirresortivo óseo de los bifosfonatos. Varios estudios de experimentación animal han confirmado esta hipótesis, constatando su efecto inhibitorio sobre el desarrollo de un camino eruptivo a través del hueso alveolar. Además del bloqueo eruptivo, las subsiguientes alteraciones del desarrollo observadas en estos dientes impactados, han confirmado la relación entre erupción y desarrollo dental como otro mecanismo posible para explicar las alteraciones del desarrollo observadas. Algún estudio (Kamoun-Goldrat A et al, 2008) constata un retraso eruptivo en niños con OI tratados con bifosfonatos de 2^a generación. Aunque el retraso eruptivo puede



considerarse un efecto secundario menor, cabría añadir también alteraciones del desarrollo a consecuencia de la impactación.

Movimiento dental. Los primeros estudios experimentales en animales se centraron en 3 problemas asociados al movimiento dental ortodóncico, el anclaje, la recidiva y la reabsorción radicular. La aplicación tanto local como sistémica de bifosfonatos mostró que favorecían el anclaje, evitaban la recidiva e inhibían la reabsorción radicular. De este modo se abría una expectativa farmacológica frente a esta problemática. Sin embargo más recientemente se ha alertado de las consecuencias de la inhibición del movimiento dental en el tratamiento ortodóncico en humanos. Al primer caso publicado (Schwartz JE, 2005) se han añadido otros nuevos (Krieguer E et al, 2013) que confirman, en pacientes adultos, los problemas encontrados a lo largo de su tratamiento ortodóncico. Problemática no suficientemente estudiada en la población maloclusiva de pacientes jóvenes con OI, tan prevalente.

Osteonecrosis de los maxilares. Curiosamente aunque este fue el primer asunto que preocupó a los clínicos que atendían pacientes jóvenes con OI, por extrapolación de los hallazgos en adultos con cáncer y metástasis óseas, hasta la fecha en las series de casos publicados no se ha descrito esta complicación en población infanto-juvenil, al menos bajo el tratamiento más común con pamidronato.

El clínico responsable de la atención bucodental del paciente con OI debe conocer en profundidad los protocolos terapéuticos administrados y la incorporación de nuevos agentes más potentes y estar al día de sus repercusiones a nivel oral y las consecuencias derivadas. Por otro lado en su relación interdisciplinar con médicos y endocrinólogos puede aportar una información específica muy útil, sobre la interacción de los tratamientos con los procesos fisiológicos orales, que podrían contribuir a modular la terapéutica aplicada de una forma más personalizada.

Dr Ricardo Sanz

Osteogenesis Imperfecta and Hearing Loss. The New Approach after Biphosphonates

Hearing impairment is not uncommon in patients with osteogenesis imperfecta. Childhood onset affects approximately 7% of children between the ages of 5 and 9, and progressive postpubertal hearing loss has been shown to occur in 40% to 60 % of patients.

All types of hearing loss are found in patients with Osteogenes Imperfecta. Conductive hearing loss is more frequently reported in younger patients and mixed conductive and sensorineural hearing loss is more commonly seen with increasing age.

The initial conductive hearing loss results from fractures of the bones of the middle ear with contracture and scarring of the incus is not unlike the fixation of the stapes or otosclerosis the most frequently ear pathology encountered.

Treatment for hearing loss in Osteogenesis Imperfecta includes a multiple pronged approach. Hearing aids and surgery are the major options depending upon the level and



type of hearing loss present.

Although Bisphosphonate therapy has not been shown to influence in sensorineural hearing loss, can increase the fixation of the stapes footplate producing an increase of threshold of hearing. The laser stapedotomy can be done and the results don't differ from the normal population. Hearing aids can be used in some cases to palliate the impairment of speech perception if no surgical alternative exists.

In profound hearing loss or deaf patients, the Cochlear Implantation is the only possibility to improve the hearing and speech comprehension. In patients with OI is relatively rare, with a few case reports published, but this is not only technically possible but the results are similar to implants outcomes for patients with sensorineural hearing loss from a variety of other causes.

14h30 - Session III - powered by Care4BB Foundation:

New Projects and Developments in Osteogenesis Imperfecta

Moderator - **Dr Patrícia Dias**

Luisa Barros, Margarida Custódio dos Santos and Ana Filipa Pires

PainLess - the Youngest Take Control

Pain is a constant burden in the lives of young people with osteogenesis imperfecta (OI) and it has been identified as one of the central issues related to their Quality of Life. Although medical treatment plays a major role in the management of OI, psychological strategies are critical components of this plan. Although most individuals with OI receive adequate medical care, most do not have access to basic education about behavioral and cognitive strategies, including pain management, which has been shown to make a difference to the lives of other young people with chronic pain. These patients are often geographically far from specialized services and traveling may be a supplementary burden.

Cognitive-behavioral pain management programs have been shown to be effective as an adjunct to medication to reduce pain, dysfunction, emotional disturbance, and school/work absenteeism, and to improve quality of life, perception of control and self-efficacy. Online pain coping programs are both innovative and a more attractive option for adolescents, whose acceptance of face-to-face intervention is not optimal, also contributing to overcome common methodological limitations such as geographic and economic barriers. Randomized controlled trials with young people who experience chronic pain were conducted to evaluate the use of Internet Self-Management Programs' and evidenced very encouraging results. No similar studies have been conducted with OI patients.

We adapted an online pain control program to reduce pain and wellbeing, and increase autonomy and perception of control in youth with OI, and conducted a pilot study in 3



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countries, Portugal, Spain and England, to test the acceptability, satisfaction and usability of the program.

Although some difficulties in dissemination and participation were identified, those who participated reported adequate acceptability and relevant benefits. Some factors that might have contributed to the poor participation are discussed, and participants' suggestions for improvement are presented.

Dr Markus Bastir

3D Morphometrics of Breathing Kinematics and its Potential Implications for Respiratory Issues in OI

In healthy subjects, the ribcage expands and contracts during respiration as a result of the interaction between the morphology of the ribs, the costo-vertebral articulations and respiratory muscle anatomy and activity. Variations in these factors are said to produce differences in the kinematics of the upper thorax and the lower thorax, but the extent and nature of any such differences and its functional implications have not yet been quantified. In order to do so this paper uses Geometric morphometrics, the statistical analysis of Cartesian landmark coordinates, a methodology that allows for separate analysis of size and shape. Applying geometric morphometrics we measured 402 three-dimensional (3D) landmarks and semilandmarks of 3D models built from computed tomographic scans of thoraces of 20 adult subjects in maximal forced inspiration (FI) and expiration (FE).

We addressed the hypothesis that upper and lower parts of the ribcage differ in kinematics (size and 3D shape changes) and compared different models of functional compartmentalization. During inspiration the thorax superior to the level of the sixth ribs performs an antero-posterior expansion that differs significantly from a medio-lateral expansion of thorax below this level. This supports previous suggestions for dividing the thorax into a pulmonary and diaphragmatic part. While both compartments differed significantly in mean size and shape during FE and FI, the size changes in the lower compartment were significantly larger. Additionally, for the same degree of kinematic shape change, the pulmonary thorax changed less in size than the diaphragmatic thorax. Therefore, variations in the form and function of the diaphragmatic thorax will have a strong impact on respiratory function.

This functional compartmentalization has important implications for understanding respiratory function in patients of Osteogenesis imperfecta, where drastically reduced mobility in the upper ribs (pulmonary thorax) has been suggested. On the basis of external chest movement analysis it has been speculated that respiratory mechanics are driven to a major extent by diaphragmatic and abdominal breathing muscles and no study has yet provided data about internal, skeletal movements of the skeletal thorax. Our project will provide new information on these issues.

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PI10/02089 (Fondo de Investigación Sanitaria) Ministry of Health, Spain. AHUCE (Asociación de Huesos de Cristal de España).

Dr Clara I. Rodríguez

Stem-Cells: Application to the Treatment of Osteogenesis Imperfecta

Adult stem cells, found in most human tissues, enables our bodies to grow and replace damaged or aging cells, since adult stem cells are believed to be responsible for growth, wound healing, and replacing cells lost both through daily wear and tear as well as from pathological conditions. One type of adult cells which are relatively easy to isolate, expand and differentiate to mesenchymal origin cells such as adipocytes, chondrocytes and osteoblasts, under controlled culture conditions, are human mesenchymal stem cells (hMSCs).

These cells have the ability to migrate to sites of injury, to modulate immune responses and inhibit inflammatory responses. These functions make the cells fundamental tools for potential cell therapy of certain diseases. In addition, MSCs have low immunogenic profiles which prevent them from being rejected during allogeneic transplantation.

Until now, hMSCs have been used in quite a few patients in various clinical trials for more than 15 years without adverse effects reported, making them a seemingly safe treatment.

MSCs infusions experiments in mouse models of Osteogenesis Imperfecta (OI) have reported a significant reduction in fracture numbers and in skeletal abnormalities, as well as an increase in bone length with a positive impact on growth. The first OI clinical trials conducted in pediatric patients suffering OI type III were quite encouraging, in spite the low engraftment observed. We are conducting an independent, multi-center cell therapy clinical trial that started in April 2014. The principal aim of this clinical trial is to assess primarily the safety and secondarily the effectiveness of non-mutated HLA histocompatible mesenchymal stem cell transplantation for OI pediatric patients irrespective of treatment with bisphosphonates.

16h00 - Session IV - powered by OIFE:

International Networks and Cooperation in Osteogenesis Imperfecta

Moderator - Ms Ute Wallentin

Ms Ingunn Westerheim

European Reference Networks - the Patient Organization's Perspective

It can be a challenge to get specialised treatment and advice for patients with rare diseases like OI. The challenge is due the lack of expertise and to the small size of patient populations across the EU.



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More collaboration between EU Member States can support a stronger concentration of expertise and make it easier for healthcare professionals to share knowledge across borders. By ensuring doctors have the most recent and expert knowledge possible, they will be better informed to make decisions on how to adapt treatment and care pathways. This in turn contributes to improvements in clinical outcomes and the quality of life of people living with a rare disease like OI. The purpose behind the establishment of European Reference Networks (ERNs) is to create a clear *governance structure* for knowledge sharing and care coordination across the EU. ERNs are supposed to be networks of healthcare providers (HCP) that are organised across borders.

Osteogenesis Imperfecta Federation Europe (OIFE) is a member of EURORDIS, which is an umbrella of patient organisations representing more than 700 rare disease patient organisations in more than 60 countries. EURORDIS started its work on ERNs in 2006. ERNs were supposed to improve access to diagnosis and treatment as well as the provision of high-quality healthcare for patients with rare diseases, which require a particular concentration of resources or expertise.

EURORDIS have together with the European Commission developed guidelines for the assessment of networks that apply to become ERNs. Since it is unfeasible to create a separate ERN for every one of the over 6000 rare diseases that exist; ERNs will be organised according to 20 different disease groupings. OI is placed in the group of "Rare Bone Disorders" (BOND).

There are no ERNs existing at the moment, but the process to establish the networks has started. An application to form an ERN for rare bone disorders (BOND) was sent in June 2016. The EU Commission will decide about approval during 2016 and the network will be established in 2017. The BOND initiative is lead by Dr Luca Sangiorgi from Bologna, Italy.

Due to the complexity and low prevalence of rare diseases, as well as to the limited body of knowledge, experience and expertise in the field of rare diseases, the role of rare disease patients (as experts in their diseases) is more fundamental in the development of the ERNs. The networks have to demonstrate they are patient-centred and empower patients as defined in the European Commission Decision.

Prof Nicholas Bishop

European Reference Networks - the Professionals' Perspective

The Rare Bone Disease ERN – "BOND"

The creation of European Reference Networks has taken 10 years so far. They are established "by Directive", so unlike the scientific programmes of research funded by the EU that are typically limited to 5 years, the ERNs will continue to grow and develop over the years to come.

The purpose of the ERNs is to improve the standard of care for patients with rare diseases; hence patients and patient organisations have a central role in determining the work undertaken by each ERN. Organisations representing patients with



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osteogenesis imperfecta such as OIFE, BBS and AOI have already contributed to the development of the plans of work that are being proposed by BOND.

A central part of this work is around OI. Within the first 2 years of the establishment of BOND, we expect to develop consensus guidelines based on the best available evidence, for the care of both adults and children with OI, across the whole range of severity and problems faced at home, in school and at work. This will only be possible with the close cooperation of patients and patient groups.

The presentation will explain the structure of the BOND ERN, the plans for its work over the next 2 years, and discuss the involvement of patients and patient groups in the development of meaningful standards of care.

Ms. María Barbero

International Cooperation in Osteogenesis Imperfecta: The OI Patient-Network

The activities the **OI Patient-Network** show that the coordinated efforts of patient organizations can be useful for both medical professionals and patients to:

- Increase the **knowledge on OI** for healthcare professionals
- Establish **international peer-cooperations** among medical professionals working with OI
- Provide people affected by OI with **state-of-the-art medical treatment** in order to extraordinarily improve their quality of life
- **Empowering OI people** and OI families all around the globe
- **Educate** society and health care professionals on the special needs of OI patients

Working OI-treatment units and projects on international cooperation all around the world will be presented, as well as the requisites needed locally in order to organize new treatment units in countries with insufficient medical infrastructures to attend the necessities of OI patients and their families.

October 8th

09h00 - Session V - powered by Fundación AHUCE:

Orthopaedic Surgery, Physical Therapy and other Challenges

Moderator - **Dr Carolina Escalda**

Dr Suken A. Shah

Management of Spinal Conditions in Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a genetic disorder of type I collagen. Type I collagen is located mainly in bone, ligaments, dentin and sclerae. There are multiple genotypes and



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phenotypes associated with OI; about 90% of the mutations are in the COL1A1 and COL1A2 genes. OI is characterized by bone fragility and patients typically present with multiple fractures or limb deformity; however, the spine of patients with OI can also be affected.

Spine manifestations of OI include scoliosis, kyphosis, craniocervical junction problems and spondylolisthesis in the lumbosacral spine. The early use of bisphosphonate treatment has been shown to be beneficial for the extremities and the spine by decreasing progression of scoliosis and improving bone quality. Patients should be screened with a clinical exam, including neurologic exam and a lateral cervical spine x-ray by school age to identify silent craniocervical junction abnormalities such as basilar impression. The incidence of lumbosacral spondylolysis and spondylolisthesis is higher in OI than the general population. Contemporary operative techniques such as traction, pedicle screw instrumentation, cement augmentation and use of antifibrinolytics to decrease blood loss have advanced the treatment of these children with severe spinal deformity. The importance of early identification of scoliosis, kyphosis and craniocervical junction problems cannot be over emphasized.

Dr Ana Bueno Sánchez

New Techniques in Orthopaedic Surgery

La actitud médica ante la OI parece que va cambiando, incluso quirúrgicamente. Los traumatólogos, en general, también consideran más veces el tratamiento quirúrgico como método para no empeorar e incluso para mejorar la situación física y la independencia de los pacientes con OI. El tratamiento quirúrgico acorta el tiempo de inmovilización, de descarga y de reposo. Evita consolidaciones viciosas. Aumenta la resistencia del hueso de forma primaria y secundaria y contiene fracturas evitando que se desplacen y por lo tanto en este sentido evita otras cirugías.

La indicación quirúrgica en un paciente con OI, aún siendo un niño, o con mayor motivo, por serlo, está más veces indicada que en un niño sin OI. Sin embargo, no siempre hay que operar. Sólo aquellas fracturas en las que el tratamiento ortopédico suponga un retraso en el apoyo, una inmovilización prolongada o un defecto en el eje carga.

A la hora de realizar el tratamiento quirúrgico, el cirujano responsable también debe valorar su conocimiento y su experiencia respecto al frágil y especial comportamiento biológico del hueso con OI. La técnica quirúrgica debe anticiparse a la respuesta del hueso, es decir, anticiparse para evitar complicaciones secundarias a la propia cirugía. Esto es, una nueva fractura. Las características biomecánicas del hueso con OI no permiten el mismo tratamiento ortopédico ó quirúrgico que aplicaríamos en un hueso sano ante la misma fractura.

Hoy sabemos cómo estabilizar las fracturas sin el riesgo a fracturas nuevas.

En los huesos largos no se deben usar fijadores externos ni placas porque facilitan la fractura en las corticales donde se asientan. La síntesis debe ser intramedular de epífisis a epífisis, sin apoyo en las corticales y telescopable en los niños. En adultos también



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debe evitar el apoyo en las corticales. La cirugía en las zonas epifiso-metafisarias también deben evitar las placas. En la cadera, la técnica de elección es la descrita por Wagner para la coxa vara congénita.

En algunas situaciones de alteración en los ejes próximos a la articulación o en ciertas discrepancias de longitud, la calidad del hueso permite aplicar las modernas técnicas de crecimiento guiado con placas en el cartílago de crecimiento.

En disimetrías más importantes, se están empleando distintas técnicas quirúrgicas, e incluso técnicas híbridas de alargamientos: alargamiento progresivo con fijador externo y clavo intramedular.

La columna vertebral (CV) es un reto abordable. Correctamente abordable actualmente en manos expertas. En la cirugía de las deformidades de la CV se debe tener en cuenta, los siguientes parámetros: la laxitud del paciente, los aplastamientos asociados, el grado de rotación, el tamaño reducido de los pedículos, la edad del paciente, el grado y tipo de curva y la fragilidad del hueso. A pesar de su dificultad sabemos que se deben instrumentar un número mayor de pedículos, que se deben ampliar los niveles para no caer en el tránsito de las curvas y que la instrumentación usada no se debe anclar en las costillas.

La patología quirúrgica cervical o la occipito-axoidea, son patologías poco operadas hasta ahora. Sin embargo, a pesar de las dificultades y de los riesgos, actualmente sabemos que deben ser tratadas, porque muchos niños y adultos disfrutan de un grado de independencia no imaginable hace unos años, al cual no deben renunciar.

A pesar de todo lo avanzado en el conocimiento de la enfermedad y de su comportamiento quirúrgico, la cirugía no ha sido capaz de resolver situaciones anatómicas muy limitantes como la protrusión acetabular. Tampoco ha podido resolver con mejor éxito los terribles pies planos, valgus, pronados asociados sobre todo a la hiperlaxitud de muchos pacientes. El uso de prótesis subtalares asociadas al retensado ligamentoso o tendinoso no han resultado ser tan eficaz porque el pie tiene numerosas articulaciones todas ellas con idéntica laxitud y deformidad al apoyo.

Todas estas cirugías que deben practicarse para mejorar o al menos para no empeorar la situación física del paciente, en general, técnicamente no son difíciles. Su complejidad radica en el hueso sobre el que se realizan, con su especial comportamiento biológico ante la fractura y ante la cirugía. Para aplicarlas correctamente es fundamental conocer y considerar esta realidad.

Pht Miguel Rodriguez Molina

Physiotherapy Concepts in Osteogenesis Imperfecta

Osteogenesis Imperfecta is a rare disease that requires specialized knowledge and treatment, provided by a multidisciplinary group of professionals working together to get best results. As one of the main four legs of the treatment (surgery, medical, physiotherapy and psychology), physiotherapy provides to the OI patients and to their families, treatment solutions, handling skills and responses for their physical and



musculoskeletal problems. Moreover, the role of the physiotherapist includes improving the quality of life, increasing functionality and encouraging maximum independence. However, physiotherapists found strong barriers to approach each case and a common lack of specific knowledge about the disease that can lead us to fear even when facing a treatment in a person with Osteogenesis Imperfecta. The term brittle bones does not offer a true picture of what is this disease about and leads to the creation of false myths that raise questions for the therapist, turning away from concepts such as heterogeneity, the need for movement by those affected, and their training and recovery right after the fractures. The management of these patients required for the physiotherapist specialization and knowledge of some basic concepts that will eliminate these barriers and the fear of treatment, and decrease rejection which sometimes exposed by professionals. Be clear about these concepts increases patient confidence, self-confidence of the therapist and reduces the risk of fractures and / or soft tissue lesions in these patients.

Honorary Lecture

Moderator - Dr Manuel Cassiano Neves

Prof Francis Glorieux

New Pharmaceutical Treatments

Therapeutic goals have to be tailored to the phenotype and the mobility status. In mild forms, fracture management may be sufficient. In more severe forms, the association of long bone deformities, scoliosis, reduced mobility and chronic pain call for more active intervention. The documented increase in bone resorption coupled to decreased bone formation was the rationale for using bisphosphonates. Multiple studies established that positive effects on lumbar spine BMD, vertebral body morphology, mobility and bone pain lead to improved quality of life in moderate/severe OI. A positive effect on fracture incidence is more difficult to assess in view of the variable degree of mobility and the frequent crippling deformities. The magnitude of the response appears correlated to skeletal growth thus treatment should be initiated as soon as the diagnosis is made and maintained during the whole growing period with dosage adjustment according to gain in aBMD. Because bisphosphonates remain in bone for a very long time, shorter term inactivation of bone resorption has been proposed with encouraging results using a cathepsinK inhibitor, denosumab. The possibility to promote bone formation is intuitively appealing and positive results have been reported with teriparatide in adult OI. Another approach is through antibody-mediated sclerostin inhibition. Pre-clinical studies and a short term Phase 2 trial in adult OI have been positive. Larger Phase 3 trials will be soon implemented. Because it was recently observed that TGF is overexpressed in OI, its antibody-mediated suppression was attempted in various mouse models. The results were sufficiently positive to stimulate



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the implementation of a Phase 1 trial in adult OI. Other pharmaceutical approaches will likely be proposed in the future before cell/gene therapy will become a reality.



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Oral Communications

Dr Atul Bhaskar

FRCS Tr & Orth, FRCS, M.S., M.Ch UK. Paediatric Orthopaedic Surgeon Bombay Hospital Institute of Medical Sciences

Dr Gaurav Jain

Senior Resident, Bombay Hospital Institute of Medical Sciences

Surgical treatment of Osteogenesis Imperfecta in a Developing Country with Resource Limitation: Results of Rodding and Impact on Ambulation and Refracture

Introduction

Delay in presentation and surgical intervention is not unusual in the developing world as regards treatment of OI due to various local and cultural beliefs. Most children are treated with plasters, bone plating and K wire fixation until the initial fractures heal only to be followed by a refracture. The greatest myth in treating children with OI is that most parents are counselled that “plaster treatment is sufficient” for fracture healing. The purpose of our study is to review the results of 21 children with OI cases who have been treated with sub-optimal fixation or those that have been allowed to refracture with progressive increase in deformity.

Patient and Methods

We reviewed treatment of 21 OI patients that presented at various age groups for treatment of recurrent fractures. Six children had undergone two or more surgical procedures for their fractures before referral. 28 femur and 21 tibia were rodded using a combination of Rush Rods, local Fassier Duval Rod, K wire and supplementary plating was done in 5 children (8 femur) to achieve stability. Three children in the group (5 humerus) also underwent Humeral rodding. Ambulatory status was assessed by the Hoffer and Bullock grading and muscle power was recorded using the MRC grade. Ten children had received intravenous bisphosphonates pre-operatively. Post-operatively the children were assessed for ambulatory status, pain, and ability for independent self-care

Results

The mean follow-up period was 34 months (24 – 48 months). Rush rods were used in 20 femurs, Fassier- Duval (FD) rod in 6 femur and in two cases with narrow intra-medullary canals “K” wires were used. For the tibia, 15 children received rush rods and in 6 cases a FD rod was used. The mean time to fracture union was 8 weeks (6 weeks – 12 weeks). Before surgery, 13 children were in Hoffer grade 4 (Wheel Chair independent or carried by parents in the developing country), four were able to ambulate with walking aid (Hoffer grade 3b), and 4 were able to walk about in the house without aids (Hoffer grade 2). After the rodding procedure the ambulatory status changed in 50% of children



– seven children (33%) became physiologic walkers (grade 3b), three could walk unaided with orthosis (grade 1b) and one child with mild OI could walk unaided (grade 1a) . No child had deterioration in ambulatory status. The incidence of new fractures reduced dramatically after rodding. Only two children had re-fractures at the distal end of the rod due to growth of bones. Supplementary plate fixation was done in six cases. No case of nonunion was seen but three children had asymptomatic incomplete union of their femur osteotomy. One incomplete union was seen with the humerus fixation. The mobility status and ability to function had improved in children at the latest follow-up.

Conclusions

Intramedullary rodding treatment for recurrent fractures in children with OI improves their mobility potential and prevents repeated cast application which is not only cumbersome for the children and families but also causes further osteopenia and deterioration in the quality of bone.

Despite only 50% improvement in ambulation, parents reported satisfactory outcome as the re-fracture rate reduced to almost nil. Many parents had not been told that rodding is an option for treatment for repeat fractures as reflected in the higher mean age of surgery in this study.

Increase awareness amongst doctors and caregivers is required to advocate early rodding for children with OI to prevent recurrent fractures.

Dr Ana Bueno and Dr José Ignacio Parra García

Especialistas en traumatología y Cirugía Ortopédica. H.U. de Getafe. Madrid. España

The best surgical technique in the treatment of the Hip in OI

Introduction

A review of our experience in the surgical treatment of the hip in patients with Osteogenesis Imperfecta (OI)

We value cases where the hip needs to be operated, not only when coxa vara if not also in cases of hip fractures or near to it.

We do not include other clinical cases as developmental dysplasia of the hip or paralytic injuries

Methodology

We performed 35 hip surgeries but we only included the cases operated for coxa vara or fractures. 26 cases, 15 patients, operated on in our hospital from 2000 to October 2015. In most cases we used the Wagner Method.

Results and Discussion

The coxa vera is a clinical situation present in OI and a complication of many fractures of the greater trochanter near. The Wagner method described by this author as a treatment in the correction of the idiopathic coxa vara of a child and applied by Finidori and Fassier for OI is the method of choice in the pathology of the hip in OI.

In the same way this surgical technique should be used in next few fractures the greater trochanter how prophylaxis to hip secondary injury.



Dr Ana Bueno and Dr José Ignacio Parra García

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Growth cartilage injury in surgery of the femur and tibia in OI

Objectives

We have analyzed the cases of patients with osteogenesis imperfecta treated with intramedullary nails in the long bones of the lower limbs during growth

We have analyzed the perforated physis, nail type and the appearance or not of epiphysiodesis, especially in those cases where we had to remove the nail or this is unhooked

Methods

We reviewed the patients treated surgically using the technique of intramedullary nailing for fractures or deformities. Between January 2000 and August 2016. We have performed more than 300 surgeries. The 70% in long bones of lower limbs.

We have analyzed how many of them have produced epiphysiodesis.

Results

There aren't epiphyseal lesions produced in the proximal or distal of the tibia, or distal femur. We observed some cases of coxa valga caused by the introduction of the nail by the greater trochanter. Of them only one case has been valued surgically and presented a pathological fracture.

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Quantitative ultrasound (QUS) and Dual X- ray absorptiometry (DXA) in patients affected by Osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI) is a group of genetically and clinically heterogeneous disorders of connective tissue, characterized by several bone defects and high risk of fractures. Dual X-ray absorptiometry (DXA) is still considered the "gold standard" for osteoporosis diagnosis offering available measure of bone mass. Currently also patients affected from OI are assessed by DXA scan, even though its specific limits (use of ionizing radiation and large equipment, not availability in children between 0-3 years old, high costs). To overcome DXA limits other diagnostic techniques such as Quantitative Ultrasound (QUS) have been proposed .

QUS, measuring the speed of sound and the broadband ultrasound attenuation at different skeletal sites, can investigate bone structural features and properties.



Aim of the study is to evaluate the utility of QUS technique versus DXA in patients with OI.

Materials and Methods

A cohort of 34 mild type OI patients (17 males and 17 females aged from 3 to 18 years, mean age $4 \pm 7,2$) not in treatment, attending the Congenital Osteodystrophies Centre and Bone Metabolism of Pediatrics Department of "Sapienza", University of Rome, from 2014 to 2015, have been enrolled in the study. They have been comparatively examined by DBM Sonic BP ultrasonometer (IGEA, Carpi, Italy) and HOLOGIC QDR 4500A densitometer. QUS measurements has been performed at phalanges. AD-SoS and BTT were the QUS variables measured. Bone Mineral Density (BMD) measured at the lumbar spine (from L1 to L4) by DXA scanner has been expressed as Z-score. Genetic and laboratory tests (blood count, serum and urinary creatinine, BUN, calcium and other electrolytes, ALP-2, PTH, 25-OH-D Vitamin, β -cross laps, TSH, FT3, FT4, urinary calcium) have been performed in all patients to define the genetic OI type and exclude other diseases.

Results

In all patients we found lumbar spine BMD Z-score values ranged between -1,6 and -3,1, according to the well-known bone density deficiency in mild OI.

At the same time QUS measurements, AD-SoS and BTT Z-score, were ranged respectively between -0,6 and -2,1 and between -0,9 and -0,32. Significant positive correlation was found for both AD-SoS and BTT versus BMD.

The correlation coefficient for AD-SoS vs BMD and for BTT vs BMD was respectively $r = 0,595$ ($p < 0,01$) and $r = 0,695$ ($p < 0,01$).

Conclusions

This study suggests that QUS AD-SoS and BTT are correlated with bone density and cortical area. In our patients these parameters are in accordance with bone deficiency and cortical reduction which are peculiar in OI

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Renal ultrasound screening for nephrocalcinosis in children with osteogenesis imperfecta

Background

Nephrocalcinosis secondary to hypercalciuria is a recognised complication of osteogenesis imperfecta (OI). Renal ultrasound scanning is the gold standard screening



tool to assess for this condition, however guidance regarding the necessary frequency of scanning is currently lacking. At present we aim to perform annual renal ultrasound scans for all children and young people attending our national Highly Specialised Childhood Complex *OI* Service, although recent scanning capacity issues have affected our ability to offer this. We also recognise that the yield from ultrasound scanning is often low and that the natural course of nephrocalcinosis may be benign. Therefore we are keen to review our current practice and consider if the frequency of ultrasound scanning can be safely modified.

Aim

To review the utility of renal ultrasound screening for nephrocalcinosis in children with *OI*.

Method

Eligible children who underwent renal ultrasound screening for nephrocalcinosis over a five year period from April 2011 to April 2016 were identified from our patient database. Retrospective chart review assessed the diagnostic yield and also reviewed children's *OI* type, family history, genetics if known, treatment with bisphosphonates, interval between follow up scans and urinary calcium to creatinine ratios.

Results

217 children with *OI* underwent renal ultrasound scanning during this time period. For children who had more than one scan, the average time interval between scans was 1.5 years. 9 children were identified to have nephrocalcinosis and 1 had a renal calculus detected. Of these, 1 child had Bruck syndrome, 6 had type 1 *OI*, 1 had type 3, 1 type 4 and the child with the renal stone had type 8. 4/10 children met criteria to be classified as Severe or Atypical according to our national Highly Specialised Service guidelines. Genetics were available for 4/10 – 2 children had confirmed genetic mutations in COL1A1, 1 in COL1A2 and 1 in LEPRE1. In all cases, management of nephrocalcinosis involved monitoring only. 7/10 children were currently being treated with bisphosphonates. Nephrocalcinosis had resolved by the time of subsequent scan in 4 children and reduced in a further 1. 2 children have repeat ultrasound scans awaited and 1 has subsequently transitioned to Adolescent Services. 1 child was referred to urology for an opinion due to pelvicalyceal dilatation, but no intervention was required. The child with the renal calculus has remained stable over time. Not all children had urinary calcium to creatinine ratios checked at each clinic visit, however from the results available, 3/10 with nephrocalcinosis had normal ratios and 1 child's result was low. In addition, a further 6 children with *OI* who underwent interval monitoring investigations had high urinary calcium to creatinine ratios detected during this time frame and interestingly none of these had nephrocalcinosis on subsequent renal ultrasound scans.

Conclusion

Renal ultrasound scanning remains an important tool to screen children with *OI* for possible nephrocalcinosis. Our results suggest that this condition has a low incidence and relatively benign course, especially when children are being treated with bisphosphonates which are protective. Urinary calcium to creatinine ratios, although



helpful, do not always appear to correlate with nephrocalcinosis on ultrasound scan. Further study is required to assess the full population of children attending our Highly Specialised OI Service and define the optimum time interval for screening renal ultrasound scans.

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Treatment with neridronate in adults and children with Osteogenesis Imperfecta: Data from Open-label, not controlled, three-year italian study

Neridronate is an amino-bisphosphonate licensed in Italy for the treatment of osteogenesis imperfecta (OI). The aim of our study was to assess the long-term efficacy and safety of this treatment in patients with OI.

The patients enrolled were divided by age into two groups: 55 patients younger than 20 years old (included) and 114 patients older than 20 years old. Both groups were observed for 3 years. Neridronate was administered by i.v. infusion at the dosage of 2 mg/kg, up to a maximum of 100 mg at three-monthly intervals for three years. Dual X-ray absorptiometry of the lumbar spine, hip and ultradistal and proximal radius were evaluated every 6 months. Blood calcium, phosphate, albumin, fasting urinary calcium/creatinine ratio, urinary free-deoxy pyridinoline and serum bone alkaline phosphatase were obtained at baseline and every 3 months.

The mean lumbar spine and total hip BMD significantly and progressively increased from baseline up to month 36 in both patients groups. The mean lumbar spine and total hip BMC significantly increased to any time point from baseline up to month 36 in both patients groups. The mean ultradistal radius BMD significantly increased from baseline to any time point in patients younger than 20 years, while, in patients older than 20 years, BMD significantly increased from baseline only at month 18, 30 and 36 respectively. The mean ultradistal radius BMC significantly increased from baseline to any time point in patients younger than 20 years, while there were no substantial or statistically significant changes from baseline to any time point in patients older than 20 years. The mean proximal radius BMD significantly increased from baseline in the period ranging from month 18 to month 36 in patients younger than 20 years. On the contrary, there were no substantial or statistically significant changes from baseline at the other time points, as well as there were no substantial or statistically significant changes from baseline at any time point in patients aged older than 20 years. The mean proximal radius BMC significantly increased from baseline to any time point in patients younger than 20 years ($p < 0.001$ at all times, except $p = 0.005$ at month 6), while there were no substantial or statistically significant changes from baseline to any time point in patients



aged older than 20 years. The mean number of fractures observed in the 3 years of treatment was significantly lower than that observed in the 3 years before the start of treatment in both groups. Adverse drug reactions (ADRs) were reported in 31 patients (56.4%) younger than 20 years and in 29 patients (25.4%) older than 20 years. Most of AEs were symptoms of an acute phase reaction, which was reported in 47.3% of patients younger than 20 years and in 22.8% of those older than 20 years. Serious adverse events (SAEs) were reported in 19 patients (34.5%) younger than 20 years and in 26 patients (22.8%) aged older than 20 years. None of the reported SAEs in both groups was considered as treatment-related.

Conclusions

Long-term treatment with i.v.neridronate has positive effects on BMD, BMC, bone turnover markers and fracture risk with a good safety profile in both groups.

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Sternal geometry, ventilatory and thoraco-abdominal pattern in children with Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a congenital disease characterized by bones fragility and progressive deformity. Life expectancy is impaired in the non-lethal most severe type III form particularly before the age of 10 years[1–3]. The main cause of death in OI is respiratory insufficiency resulting from impaired thoracic and pulmonary function. We have previously shown that structural modifications of the ribcage, i.e.: reduced sternal angle or pectus carinatum, is typical in adult type III and it has important consequences on ventilation and chest wall function. In fact type III patients are characterized by paradoxical inward movement of the pulmonary ribcage during spontaneous breathing at rest (QB) in supine position that leads to shallow breathing. This is a costly way to breathe because the contraction of the respiratory muscles is partially wasted to distort the ribcage and not to inflate the lungs [4].

Our aim is therefore to study sternal geometry, ventilatory and thoraco-abdominal pattern during QB in OI children younger than the age of 10. As sternal deformity is congenital, our hypothesis is that the severity-related profile of respiratory function, found within the different OI subtypes of adults, may be present since childhood.

Seven type III (median age: 6.2 years, interquartile range: 2-9), 8 type IV-V (6.6 years, IQR: 4-11) and 9 healthy children (7.3 years, IQR: 5-9) younger than the age of 10 were enrolled and analyzed. Sternal geometry, ventilatory and thoraco-abdominal pattern during QB were assessed in supine position in a non-invasive and non-volitional way using opto-electronic plethysmography [4,5].

Data are reported as median and interquartile range (IQR). Significance was set from $p < 0.05$.



The transversal angle at the sternum in type III (151.3°, IQR: 139.4-164.4) is significantly ($p < 0.05$) lower than type IV-V (173.4°, IQR: 162.1-182.3) and healthy (169.6°, IQR: 164-175) children. Pectus carinatum is therefore a feature of type III OI since childhood.

Type III children are also characterized by rapid and shallow breathing: their breathing frequency (RR: 37.9 min⁻¹, IQR: 33.1-43.7) and tidal volume (VT: 94 mL, IQR: 80-114) are respectively significantly ($p < 0.05$) higher and lower than healthy (RR: 22.7 min⁻¹, IQR: 18.9-25.1; VT: 174 mL, IQR: 111-263) peers. Tidal volume is reduced because the pulmonary rib cage contribution to tidal volume (%VRCP: 3.4%; IQR: 2.8-8.7) is lower ($p < 0.05$) than type IV-V (%VRCP: 10.5%; IQR: 7.2-16.9) and healthy (%VRCP: 24.8%; IQR: 16.4-27.2) children. %VRCP is an index of the action of intercostal muscles that therefore is reduced in these children, while the diaphragm is preserved and leads inspiration.

Type IV-V children show normal breathing frequency (RR: 26.3 min⁻¹, IQR: 25.7-27.2) and tidal volume (VT: 138 mL, IQR: 125-146), reduced %VRCP and absence of sternal deformity like healthy peers and adult type IV4.

Five type III patients were analyzed at least twice in the last 8 years according to their hospitalization and therefore it is possible to study the evolution with age of %VRCP and sternal angle in these children.

While sternal angle is always within the range found in adult type III, %VRCP starts below the range of healthy children and then it linearly declines with age towards negative values (index of paradoxical inspiratory inward movement), to approach the range of adulthood type III [4].

We can conclude that, an altered breathing pattern in OI type III is present since childhood characterized by rapid and shallow breathing with poor action of the intercostal muscles without paradoxical thoraco-abdominal movement. These results suggest that the presence of pectus carinatum, per se, puts the intercostal muscles in mechanical disadvantage resulting in shallow breathing. %VRCP progressively declines with age toward negative values and therefore the restrictive thoracic pattern worsens.

While pectus carinatum is congenital, scoliosis starts to be severe at the end of childhood in OI [6]. We can speculate that the combination of sternal and spinal deformities represents such an additional load for intercostal muscles, that they become no more able to counteract the action of the diaphragm. This results into the onset of inward paradoxical movement during inspiration, being a costly way to breathe.

Moreover, it seems that earlier achievement of paradoxical thoracic movement at rest in supine position could predict development of pulmonary complication, as the only child with negative %VRCP died at the age of 9, but further studies are needed to confirm this consideration.

Type IV-V children show absence of sternal deformity, normal ventilatory pattern and slightly reduced intercostal muscles action maybe due to ribs softer than healthy peers. These results confirm that, according to the severity, the ventilatory and thoraco-abdominal patterns are different in OI since childhood. In OI type III the assessment of



the respiratory function should therefore start in early childhood, with great attention to the thoraco-abdominal contribution and synchrony, in order to try to reduce the incidence of premature death.

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Abstracts

Poster Sessions

Group 1

Moderators: Dr Patrícia Dias and Dr Joaquín de Nova

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Rare Commons: an online platform to facilitate clinical research in Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a genetic disorder that affects the production of collagen and is characterized by bone fragility. It encompasses a wide phenotype and genotype spectrum as well as a highly variable degree of severity. Its estimated incidence is 1 per 20.000 births, which qualifies it as a rare disease. One of the major challenges in research of rare diseases is to achieve a large and representative cohort of patients. Conversely, patients and their families are a source of invaluable knowledge that allows investigators to better understand these diseases. In recent years, Internet and specifically Social Networks have revealed its potential use for sharing experiences, which demonstrates that patients and families want to take an active role in the care and knowledge of their disease.

Rare Commons (RC) is a research project based on an online platform (www.rarecommons.org) which allows obtaining reliable, rigorous and updated information on a particular rare disease, thanks to a dynamic format modeled on virtual social networks, leaded by an expert team in a secure environment and building upon information, learning and participation. OI users will be grouped into a private community that will bring together families and the community of physicians and researchers. Families will be empowered through high quality patient addressed scientific chapters about OI and they will be offered the opportunity to fill in exhaustive



questionnaires about their disease. During the different stages of the research project, patients and families will have the help and collaboration of the Patient Advocacy Manager of RC.

The OI project is designed to provide mutual support between families and physicians. The platform allows users to participate in different languages (including always Spanish and English). Thanks to its international scope, the RC project allows for the study of the largest possible number of children worldwide affected by OI. This aspect is essential to achieve representative cohorts and statistically reliable results which otherwise, in rare diseases, is very difficult with other methods of recruitment.

OI clinical research project has been approved by the Clinical Research Ethics Committee of Sant Joan de Déu Children's Hospital and fulfills regulatory international laws regarding Data Protection.

The project is designed in three phases: Phase 1: Implementing the online interface than includes the development of: 1) educational resources in OI with exhaustive and comprehensive information, divided into easy reading medical chapters and available for participating families; 2) detailed clinical questionnaires that patients/families will fill in with information of their disease (including clinical, laboratory, radiological, genetic and therapeutic data). Phase 2: Recruitment of patients through contact with patient associations from different countries and through the social media tools of RC. Phase 3: Inclusion data, subsequent biomedical analysis and scientific publications.

Launching an online platform as RC will enable to dispose very valuable information on OI which will lead to the development of multiple lines of investigation.

(Poster in next page)

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Somatic COL1A1 mosaicism in a newborn with Osteogenesis Imperfecta

Background

Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder characterized by increased bone fragility and low bone mass. The different types of OI may be distinguished by their clinical features and the causative genes, with *COL1A1* and *COL1A2* genes as the most frequent. The guidelines for OI genetic diagnosis first recommends the screening of *COL1A1* and *COL1A2* genes using Sanger sequencing. However, this method has limitations to detect somatic mutations with low allele frequency, which could be overcome with the use of Next generation sequencing (NGS) technologies.

Presenting problem



We describe an infant born from a bichorionic twin gestation at 33 weeks. At 8 days of life, she presented displaced right femur fracture. The skeletal series also revealed ribs fractures and thoracic vertebral compression. Bone metabolism screening was normal. Despite no familial history of OI was registered and no other features of OI were detected, a genetic study was performed.

Clinical management

COL1A1 and *COL1A2* genes were screened using Sanger sequencing. The analysis of *COL1A1* detected the c.1129G>A transition, which generates the already known p.Gly377Ser mutation. However, analyses of chromatograms revealed a marked disbalanced fluorescence intensities among wild-type and mutated alleles, suggesting a potential somatic *COL1A1* mosaicism. To address this issue, we performed targeted deep sequencing using genomic DNA extracted from blood and mucosal swabs. This analysis revealed the c.1129G>A mutation in both samples at a similar allele frequency (25%). The mutation was not detected in patient's parents, supporting its *de novo* nature. The patient started treatment with pamidronate, calcium and vitamin D, and no fractures occurred during 20 months of follow-up.

Discussion

We describe the first case of somatic *COL1A1* mosaicism causing OI. Due to the relatively high frequency of the mutated allele, Sanger sequencing was able to detect it and NGS technologies finally confirmed and quantified the degree of mosaicism. This approach enabled us to definitively diagnose this patient, and support NGS as the recommended technology to evaluate gene mosaicism.

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Osteogenesis imperfecta in one gemellus from the twin-pregnancy after in vitro fertilisation

Osteogenesis imperfecta is a variable and rare disorder. It is caused by a mutation of a gene which negatively impacts building of the connective tissue. Its major feature is a fragile skeleton, but many other body systems are also affected. Our patient was born as a preterm infant, in a 34 weeks of gestation, with low birth weight. It was a twin pregnancy after in vitro fertilization that was succesful at the 7th attempt of the embryotransfer, he was gemellus A. He is a child of unrelated parents. Delivery was acheived through Cesarean section. His stay at NICU was uncomplicated. Dismissal was at the age of 25 days. Then suddenly one week later, a painful swollen left tight appeared. He was admitted to our department. His skull was soft, with enlarged great fontanelle and wide sutures. He had a very light blue sclera. Whole body X-rays revealed



multiple fractures, compressive vertebral fractures and the skeleton with diffuse decalcination. Targeted genetic tests were run, missense mutation of COL1A2 gene (c.1972?A.p., Gly658Ser) was found. It is the first case in this family, this mutation was evaluated as de novo. The treatment with intravenous bisphosphonates has been initiated at the age of 2 months in cycles of 3 days repeated every 10 weeks. Till today he has been given 7 cycles already. Besides the pamidronate he also receives adequate supplementation of D vitamin and calcium. He is examined by a neurologist and a cardiologist every 3 months, including ECG and echocardiography and every 6 months by an ophthalmologist. Thanks to medicaments and a great handling care of his mother he hasn't got a fracture since the age of 2 months. Nowadays he is a happy 16 months old toddler that is developing appropriately according to his age.

(Poster in next page)

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Sensory Integration Dysfunction in Osteogenesis Imperfecta: A Case Study

Introduction

Sensory Integration is a neurological process involving the reception, registration, modulation, organisation and interpretation of sensory information. Trauma and limited opportunities in early life are hypothesised to impact on the development of sound sensory integration. Impairments in this sensory processing can lead to deficits in the planning and production of purposeful movements and behaviours. Within childhood Osteogenesis Imperfecta (OI), therapy is typically based on a biomechanical approach. Sensory Integration is yet to be explored as an approach to assessment and intervention

Case Presentation

Child X is a 9 year old boy diagnosed with Osteogenesis Imperfecta (OI). He presented at age 5 having experienced several fractures including tibias, elbow and ankle. Vertebral compression fractures of T1 and T5-T8 were evident. DEXA scan showed a lumbar bone mineral density age matched Z score of -3.3. On clinical examination he was also noted to have blue sclera, marked ligamentous laxity and reported easy fatigue.

Subsequently, Child X received Pamidronate infusions at 3 monthly intervals for 4 years. Bone mineral density aged matched Z score is now -0.8. He has had no further fractures. Child X continues to present with marked ligamentous laxity. He stands with a hyperlordotic posture and pes planovalgus foot position. He wears bilateral dynamic ankle foot orthosis (DAFO) to provide additional support and stability to his foot position.

Child X reported a number of functional difficulties both at home and school. These included poor balance and motor co-ordination, handwriting difficulties, reduced exercise tolerance, poor personal organisation of self and belongings, and social immaturity. Both child X and parents expressed anxiety of further fractures. Child X



showed a preference for sedentary activities, avoiding anything perceived as challenging or unsafe. These functional difficulties may also be indicative of sensory integration dysfunction.

The Sensory Processing Measure (SPM, Parham et al 2007) and Sensory Integration and Praxis Test (SIPT, Ayres 1989) were used to measure sensory responsiveness, praxis and discriminatory functions. The SPM is a questionnaire style form completed by parents and teachers. The SIPT is a standardised measure completed by the therapist in a clinic environment. No difficulties with sensory modulation were identified on the SPM. Results from the SIPT showed a pattern of dysfunction consistent with somatodyspraxia, attributable to difficulties in the proprioceptive and vestibular systems. This pattern of dysfunction impedes development of independence in daily routines and is strongly associated with poor social skills.

Discussion

This case of a child diagnosed with OI presenting with difficulties characteristic of sensory integration dysfunction suggests a new paradigm for sensory integration development in the presence of musculoskeletal abnormalities. Development of effective Sensory integration is influenced by early childhood experiences. Movement experiences are key to the foundations of vestibular-proprioceptive systems. Immobilisation and motor delays following fracture may hamper this. As shown in a systematic review by Smith et al (2013), proprioception is reduced in hypermobile joints, a common clinical feature of Osteogenesis Imperfecta. Functional challenges resulting from sensory integration dysfunction can include the planning and production of purposeful motor skills. Further research in a larger group is required to investigate if Sensory Integration is a contributing factor to the functional challenges of the OI population. Using such an approach may offer further treatment opportunities to promote functional independence in children with OI.

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Bruck Syndrome in a Mozambican patient with a homozygous mutation in FKBP10 gene

Introduction

Bruck Syndrome (BS) (OMIM %259450 and #609220) is a rare autosomal recessive disorder that is phenotypically related to Osteogenesis Imperfecta (OI). It is clinically characterized by congenital joint contractures with pterygia, bone fragility, postnatal short stature, limb deformities and progressive scoliosis. There are two types of BS: BS type 1 (BS 1) and BS type 2 (BS 2), which are phenotypically and biochemically indistinguishable, but share a common molecular defect: an aberrant cross-linking of



bone collagen owing to underhydroxylation. BS 1 and BS2 are caused by variants in two different genes – *PLOD2* and *FKBP10*, respectively. It has been proposed that mutations in *FKBP10* gene may be associated with a moderately severe OI phenotype in patients with BS 1, which might be a variant of the larger OI spectrum.

Here we report a Mozambican patient with a clinical diagnosis of BS due to a homozygous deletion in *FKBP10* gene, and compare this patient's phenotype with other seven cases of the literature with the same mutation.

Clinical Vignette

The patient is the only child of a non-consanguineous Mozambican couple, and the first case in her family. She was born at term, after an uneventful pregnancy. She presented at 3 years old with a history of congenital left coxa vara, mild contracture of the left knee and congenital bilateral flexion contracture of the elbows, with limited range of motion of these joints. She has short stature (< 5th Percentile) with an accentuated lumbar hyperlordotic attitude, a triangular face and small joint hyperlaxity. There is no evidence of abnormalities of the teeth or sclerae and also no hearing loss. The radiographic screening revealed a dysplasia of the left acetabulum with subluxation of the left femoral head, which required orthopaedic surgery. Until now, she had two fractures of long bones: one fracture of the left tibia and one subtrochanteric fracture of the right femur. The study of phosphocalcic metabolism is normal and the bone mineral density is low (Z-score -2,4), suggestive of osteopaenia/osteoporosis. Although her motor and cognitive development has been normal, she now ambulates aided with crutches due to a leg length alignment asymmetry.

The presence of congenital joint contractures and bone fragility lead to the clinical diagnosis of Bruck Syndrome. First, we performed the sequencing analysis of *PLOD2* gene, which was negative for pathogenic variants. Then, the sequencing analysis of *FKBP10* gene revealed a homozygous 1-base-pair duplication (c.831dup), which is predicted to lead to a frameshift mutation and premature protein truncation, thus confirming the clinical diagnosis. Parental studies are still ongoing.

Discussion and conclusion

To our knowledge, seven other patients with this mutation in *FKBP10* gene were described in the literature: 3 siblings of American-Mexican origin, 1 patient from Turkey, 1 patient from Saudi Arabia and 2 siblings from South Africa. It is interesting to notice that our patient is from the same geographic area of the latter two patients. All patients have congenital joint contractures and multiple fractures, even though these occurred at a later age in our patient. The identification of the pathogenic variant in this case is important not only for the patient, allowing a better management of the disease, but also for her family members at risk. The confirmation of the parents' carrier status will enable prenatal diagnosis and preimplantation genetic diagnosis in future pregnancies as well as carrier testing for other family members at risk.

(Poster in next page)



Group 2

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Osteopathic Manipulative Treatment Effects on Bone Mineral Density and Quality of Life in OI Adults treated with Neridronate

Background

Osteogenesis imperfecta (OI) represents a heterogeneous group of inherited connective tissue disorders caused by mutations of type 1 collagen genes (COL1A1 and COL1A2), resulting in bone fragility and skeletal deformities associated with ligamentous laxity and muscular hypotonia [1]. Nowadays, the main effective drug treatment is represented by intravenous administration of bisphosphonates in order to increase bone apposition. Generally, after 1 year of therapy and a period of relative wellbeing, treated OI adults patients experience diffuse pain, chronic fatigue and mobility disorders, possibly due to the fact that the bone mineral density (BMD) reaches a plateau [2].

Osteopathy is a rational treatment born in the United States at the urging of Andrew Taylor Still and it is based on three mechanical principles: the principle of self-healing, the unity of the body and the interrelation between structure and function. When blood, lymph and other fluids flow without obstacles, tissues can exert their physiologic functions without interference, and given the fact that any system is interrelated anatomically, functionally and biochemically through the fascia, the restoring process of a musculoskeletal dysfunction could not be exclusively attribute to a restoration of biomechanics, but it must take into account the evaluation of all the connected structures. In this perspective the OMT may contribute in bone apposition and pain reduction, promoting the withdrawal of catabolites and inflammation cells, normalizing PH levels, increasing oxygen and nutrients supply [3]-[4].

Aim

the aim of the present study was to verify whether OMT could contribute to increase the bone mass in treated OI patients. Moreover we aim to verify the hypothesis that OMT would decrease chronic pain, would increase mobility and improve quality of life.

Materials and Methods

12 patients with OI types I, III, IV, treated with bisphosphonates, were recruited at the Centre for Rare Diseases of the Umberto I Hospital in Rome, Italy. Exclusion criteria



were: age <18 yrs; fractures within 60 days before T0; moderate to severe depression (measured by the Beck Depression Inventory); patients who play sports or undergo physical therapy. OMT was administered once/15 days for 6 months. Outcome measures were: BMD, bone metabolism markers (osteocalcin, alkaline phosphatase and beta cross laps) and specific rating scales to assess pain (5 Visual Numeric Scale (VNS)-extrapolated from Qualeffo 68 Scale and the pain questionnaire in people with osteoporosis), fatigue, mobility and quality of life (Qualeffo 41), perception of the health status (SF-36). A 12-items self-reported Likert scale regarding the quality, safety and effectiveness of OMT was also administered. All the participants gave their written informed consent to the study.

Results

As regards metabolic markers, Osteocalcin levels significantly increased after OMT only in OI type I ($p=0,03$). Beta cross laps and BMD did not change in any patient. Pain was significantly lower (pain questionnaire $p=0,007$), even after only 3 months of OMT treatment (VNS_{6mo} $p<0.001$). Similarly, quality of life (Qualeffo 41) ($p=0,008$) and perception of the health status (SF-36) significantly improved in the whole sample after treatment ($p=0,008$, and $p=0,008$ respectively). No significant change emerged in daily living autonomies. Patients expressed an high liking rate at the Likert Scale: only one patient referred pain during visceral techniques, but no patient reported any negative effects after treatment.

Discussion

Our data showed an improvement of quality of life as well as a reduction in pain, resulting in an increased mobility in all patients. Bone density seemed to be influenced by OMT only in OI type I. We argue that OMT, restoring biomechanical dysfunctions and reducing pain, led to a better bone apposition only in patients with a quantitative deficit of collagen and a global mobility relatively preserved (all type I patients were able to walk). The improvement of quality of life and perception of health status seems to be related to pain reduction rather than to better global motility, since they were present in all patients. Finally all the patients well tolerated OMT, without reporting any concern regarding safety.

Conclusion

Our study showed that osteopathy is effective, adequate and safe for patients with OI and it could be a valid approach to be included in the multidisciplinary team. Since OMT has been administered about 2 times a month for 6 months, it is predictable that this treatment would be also less onerous for the national health system, and for patients with OI. OI patients in fact, especially adults, usually report difficulties in carrying out rehabilitation projects or physiotherapy treatments administered 2 or more times per week.

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Is participation in children with type 1 OI influenced by wearing a DEFO?

Background

Osteogenesis Imperfecta (OI) is most commonly caused by a defect in the genes which produce type 1 collagen. Features include fractures and ligamentous laxity. Low muscle tone is often present and in conjunction with hyper-mobility can result in reduced stability. This reduced stability affects posture and movement and results in difficulties with gross and fine motor activities. Parents of children with type 1 OI often report that their child experiences frequent tripping and falling, poor handwriting, difficulties with dressing/undressing and a lack of confidence during gross motor activities. This can have an effect on their participation at home and in nursery/school. Research has established that Dynamic Elastomeric Fabric Orthoses (DEFOs) influence posture and improve stability in children with neurological disorders who present with low truncal muscle tone and they are used internationally in this population. There is no research in the use of DEFOs in children with OI, and to date they are not widely used in the United Kingdom.

Presenting Problem

Three girls aged between 3 and 7 years presented in the OI Clinic at Great Ormond Street Hospital, London with low muscle tone, hyper-mobility and poor stability. Two have a definitive diagnosis of type 1 OI and the other has some clinical features of OI.

Parents of all three reported that their child had difficulties with gross and fine motor activities and that this was having a detrimental effect on participation both at home and school.

Clinical Management

Gross and fine motor skills were assessed together with posture in sitting and standing. All assessments were videoed to allow analysis of quality of movement and posture. Structured fine motor and gross motor activities were selected for each child based on their age and ability. These activities were analysed to establish pattern of movement and timed if appropriate. Fine motor activities included pencil grasp, in-hand manipulation, bilateral coordination and hand use. Gait, balance, posture, transitions and floor mobility were also assessed and analysed. A bespoke DEFO was manufactured



for each child. Reinforcement panels which provide directional pull were added to improve stability and posture. The child was allowed 4 weeks to slowly increase wear until the DEFO was tolerated for 6-8 hours/day and then were reviewed. Assessments were repeated with the child wearing the DEFO; tasks of the initial assessment were replicated. A questionnaire was sent to the parents to explore the impact of the DEFO on participation as well as practical issues such as ease of donning and doffing, and tolerance.

Results

All three children showed improvement in gross motor and/or fine motor activities. Improved posture was evident in sitting and standing. This in conjunction with increased stability allowed improved control during fine motor tasks and the ability to maintain a more mature pencil grasp.

Parents reported that the children were more stable when wearing the DEFO, and lost their balance less. All children were described as more confident to attempt gross motor activities, such as climbing, riding a scooter and running when wearing the DEFO. Participation increased in all three children.

Discussion

Bespoke DEFOs have been shown to influence posture and stability in these children with type 1 OI as well as improve confidence to move. The reported increase in stability and confidence may be explained by improved proprioception gained by pressure provided by the orthosis. In other studies wearing sleeve orthoses have been evidenced to increase brain activation in areas where proprioceptive inputs are processed. When considering the International Classification of Functioning, Disability and Health framework, therapy is becoming increasingly directed at improvement in the participation dimension and less at body structure and activities. The use of DEFOs should be considered as an adjunct to therapy for the child with OI, as parents and therapists have found an improvement in gross motor and fine motor skills as well as in participation.

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Development of innovative orthopedic braces for the care and rehabilitation in osteogenesis imperfecta and skeletal dysplasias

In a tertiary referral Centre for neurologic and orthopedic rehabilitation, in the last decade the authors have taken care of children with spinal deformity in OI in case of pain, platyspondilia, scoliosis, lumbar kyphosis or thoracic hyperkyphosis.

Osteogenesis imperfecta like most diseases of the musculoskeletal system requires prolonged use of external orthosis as belts or braces for lower or upper limbs and trunk. This type of devices, most of the times are made by rigid structures in plastic, that to be



truly effective have to be worn for many hours a day. Braces may be prescribed in any age, from newborn to the elderly and affects a very large series of diseases. The purpose is generally to impose a correct position of the body, recovering the normal functions of interested parties. In some cases, when properly worn these systems can ensure pain reduction, correct bone development, proper blood circulation and help the patient's normal breathing.

Unfortunately, however, the high rigidity, the weight and the reduced breathability of these systems lead to overpressure on critical body parts, lack of comfort and low acceptance by patients. In addition to causing a physical discomfort these systems have also a negative psychological effect on younger patients.

In a previous study of the authors children aged 6 months to 12 years were treated because of sagittal vertebral deformity and pain in *OI*. The minimum follow-up was 1 year. A semi soft brace (Podialene[®]) was used for 8 - 18 hours/day in association with physiotherapy or swimming activity and bisphosphonates. Pain in a 0-10 Mosby pain Rating Scale decreased from a level of 8 (\pm 1 SD) at the beginning of treatment to 2 (\pm 2 SD) at the end of treatment. Scoliosis in *OI* is characterized by high frontal deformities with minimal rotation. In 22 patients aged 6 to 12 years with mild *OI* (Types I and IV) and scoliosis from 20° to 30° a bracing treatment had poor effect in 15 pts with progression of spine deformity who needed surgical correction. In the remaining patients bracing was effective in arresting progression.

This task aims to design and optimize a new generation of orthopedic braces through the combination of innovative materials and the use of rapid-prototyping techniques. In this

purpose they will use new multifunctional polymeric materials. These materials make it possible to monitor and control the main parameters which determine the interaction human-body device quality (such as sweating, temperature, contact pressure). Attention will be paid to the optimization of interface characteristics between the device and the human body (comfort). Sensor will be introduced to improve the effectiveness and the fit of these systems. In the developmental project a specific attention will be done to the final weight of these devices, in particular by using the technique of rapid-prototyping (3D printing) which provides greater customization of the object and on the other side allows the realization of lightweight reinforcing elements with modular structural properties. The re-design will allow easy customization and easy wearability to user with limited motor functions. Expected results

Through the design, selection and development of new materials and production processes will get a new generation of wearable, custom devices, able to guarantee the correct body microclimate while maintaining health benefits and increase acceptance by patients. At the same time we will try to improve wearability and best aesthetic characteristics.

(Poster in next page)



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Online self-help groups for osteogenesis imperfecta patients and their families

Osteogenesis imperfecta (OI) is a genetic disorder of type I collagen. Type I collagen is located mainly in bones, ligaments, dentin and sclerae. There are multiple genotypes and phenotypes associated with OI; about 90% of the mutations are in the COL1A1 and COL1A2 genes. OI is characterized by bone fragility and patients typically suffer multiple fractures, limb deformity or spine problems. Its estimated incidence is 1 per 20.000 births

In this poster we present our project entitled “Online self-help groups for osteogenesis imperfecta patients and their families”. Self-help groups (SHGS) are a resource that has shown significant benefits for people affected by different health problems, including rare diseases. Indeed, according to recent studies (Seebohm, Chaudhary et al. 2013), these groups represent a space of expression free from judgement, where it is possible to acquire information about the disease, increase self-esteem, learn adaptive behaviors and find emotional support.

Also, these groups promote better use of medicines and health services, help tolerate stress, favor social relations avoiding isolation, dismantle false beliefs and allow the acquisition of new skills.

This project is the first SHGS program focused on osteogenesis imperfecta. This online service will have an international impact, bringing these groups for the first time to Latin America. This is particularly important, as these groups have the advantage of becoming over time in affected associations in those communities where they do not exist.

The main objectives of the project are:

- To increase and consolidate the social relations of participants;
- To promote the assumption of responsibility for personal change;
- To intensify the perceived social and emotional support;
- To facilitate learning coping strategies for common problems in the field of OI;
- To increase the participants’ knowledge about relevant aspects of the disease, eventually inviting renowned professionals in the field of OI;
- To promote the formation of associations in communities where none exist.

Two types of SHGS will be created: groups addressed to OI patients and groups for OI patients’ family members. The groups will include participants and a psychologist, who will manage and organize the sessions. Finally, an evaluation will be carried out through questionnaires and interviews in order to assess the development of groups and the objectives achievement.



Organizers



Dr Megan Riddington, Highly Specialist Clinical Psychologist, GOSH , **Mark Heathfield**, Clinical Nurse Specialist, GOSH, **Kirsten Donnelly**, Senior Paediatric Occupational Therapist, GOSH, **Chris Clark**, Clinical Specialist Occupational Therapist, GOSH, **Faye Mason**, Senior Paediatric Physiotherapist, GOSH, **Emilie Hupin**, Senior Paediatric Physiotherapist, GOSH, **Karen Edwards**, Clinical Specialist Physiotherapist, GOSH, **Jenny Brickell**, Head of Social Work, GOSH, **Dr Susan Parekh**, Senior Lecturer/ Honorary Consultant in Paediatric Dentistry, UCL Eastman Dental Institute & GOSH, **Dr Alistair Calder**, Consultant Paediatric Radiologist, GOSH, **Professor Andreas Roposch**, Professor of Paediatric Orthopaedic Surgery, GOSH, **Dr Belinda Crowe**, Consultant in Paediatric Neurodisability, GOSH, **Dr Caroline Brain**, Consultant Paediatric Endocrinologist, GOSH, **Dr Jeremy Allgrove**, Consultant Paediatric Endocrinologist, GOSH, **Dr Catherine DeVile**, Consultant Paediatric Neurologist and Service Lead, GOSH

The London Osteogenesis Imperfecta Team: Offering Highly Specialised Tertiary Care across the South East of England

Great Ormond Street Hospital offers tertiary level care to children and young people with Osteogenesis Imperfecta (OI) across the South East of England. Having provided services to children with OI since the 1980s, GOSH became a Highly Specialised Regional Centre for OI in 2011, along with counterparts in Birmingham, Bristol and Sheffield. The Service is committed to a programme of growth and development, to promote excellence in the care of its growing patient cohort. Fielding a multidisciplinary team of experienced OI professionals, holistic care is offered to around 300 babies, children, adolescents, young people and their families, about 85 of whom are regarded as having severe, complex or atypical OI. This poster will share the structure of the GOSH Service, identify areas of innovative practice and highlight some of the challenges faced by patients and professionals. We would welcome discussion from others working within the field, and those living with the condition or its impact, about how best to provide care that builds a better future for children and families living with OI.

(Poster in next page)



Organizers



Group 3

Moderators: Dr Anabela Bandeira and Dr Pilar Gutiérrez

Castillo Rivera Alma Iris, MD, Espinoza Lesby MD

Osteogenesis Imperfecta in Honduras. Advances

The following work is a qualitative descriptive study of the creation of the clinic in Honduras osteogenesis imperfecta, a disease that until recently was not in the interest of any personal both at institutional level and at the level of the health secretary.

In 2014 for the first time in Honduras the Foundation Sun Life and with the support of the International organization OI Godfathers, medical specialists and Maria Hospital Pediatric Specialties makes the drug therapy for the treatment of OI is delivered to a group initial 8 children from different parts of the country, initiating the improvement of quality of life, promulgation of information and sharing of the disease.

Currently, the i has a record of more than 70 patients between children and adults, all from all geographical areas of the country; 15 children under 8 years receive their care with specialists in Endocrinology, Nephrology, Genetics, Orthopedics, Physical Therapy and Rehabilitation, Odontology.

Epidemiologically speaking oi patients come mostly from central and north of the country, being more frequent among males.

Patients once identified and referred to the clinic oi are initially evaluated by endocrinology are carried out anthropometric measurements, general chemistry, renal ultrasound, densitometry bone and evaluated initiate medical treatment with palmidronate which the same protocol that is used GETAFE used, obtaining a satisfactory result, reduced number of fractures up to one year in a row, so improving their bone densitometry up to two standard deviations, and shorter consolidation of fractures, so there is less downtime thereof. Posteriormente are evaluated by orthopedic examinations are requested, the type of OI is classified, and assessed that 99% warrants placing nail FD in view of its multiple fractures grotesca deformity. So far put nails rush since no we FD nails, and are assessed by simultaneously physical medicine and rehabilitation, which patients in addition to conventional physical therapy, receiving training hidroterapiA concomitantly evaluates dentistry.

We present the case of girl of 18 was initially operated at 6 years old, which by its multiple deformities did not walk, so that its many deformities in their long bones, osteotomy was performed in rosary and pinning rush, which currently conducts its daily activities, it has been integrated into society.

(Poster in next page)



Fernández, Tamara

Psychologist; AHUCE – Asociación Nacional Huesos de Cristal OI España, SP.

Psychological aspects of OI

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility and low bone mass, with a wide spectrum of clinical expression. It is a chronic rare disease with no cure.

Treatment in OI requires a coordinated multidisciplinary team approach, which have usually been focused on physical therapy, surgical interventions and medications. Unless the psychological aspects have received little attention, the psychological intervention is a strong tool to improve people with OI quality of life, and could be considered as the fourth leg of treatment in OI.

The psychological intervention goals to attend people with OI and their families are: facilitate the adaptation after OI diagnosis and other crisis situations, minimize the emotional impact, and reduce the risk of psychopathological consequences.

People with OI have to cope with both the physical, social and emotional problems associated with OI. Even though both difficulties and resources they will find are common to everybody, there are some particular characteristics in people with OI that we should consider.

The main obstacle they find is the lack of knowledge about the disease, which affects to all their life areas. Also there are some specific difficulties related to their personal, social/family, health, educational and occupational fields that often appear. People living with OI may experience different feelings: sadness, anger, fear, isolation, rejection... which can lead to anxiety or depression. Unexpected injuries, frequent hospitalizations and loss of mobility are common circumstances to face with. Relationships and family dynamics will also be affected.

To face these challenges, people with OI have many resources, strategies and abilities that can be developed and strengthen. It is essential to stay informed about OI and seek help from professionals when is needed. Developing a strong support network, including the OI community, and socialize outside the family, is a powerful resource. Some personal skills such as creativity, problem solving, confidence and autonomy, will also help facing obstacles.

Psychologist and other health care professionals can help people to detect and analyze the potential trouble areas, evaluate the emotional distress, explore their own resources and fortitudes, and promote them. All of these will be directed to help them living successfully with OI.

(Poster in next page)



Organizers



Kirsten Donnelly

Senior Paediatric Occupational Therapist, Great Ormond Street NHS Foundation Trust*

Mark Heathfield

Clinical Nurse Specialist, Great Ormond Street NHS Foundation Trust*

Dr Catherine DeVile

Consultant Neurologist, Great Ormond Street NHS Foundation Trust

Evaluation of outreach visits to new born babies with osteogenesis imperfecta

Background

Osteogenesis Imperfecta (OI) is most commonly caused by a defect in the genes that produce type 1 collagen. The presentation at birth can vary from mild to severe, with more severe features including multiple long bone fractures, limb bowing deformities, rib fractures, vertebral compression fractures, intractable bone pain, short stature, excess sweating, constipation and bruising through vessel fragility. It can be an anxiety provoking time for parents of a new born baby with severe OI, whose local maternity and paediatric centres may have limited experience of OI and its management. This regional OI service, which is one of four national centres, offers outreach visits to local hospitals and families' homes. This is to help support professionals and families in the early management of children with severe-presenting OI. These outreach visits are prior to the patient's first multidisciplinary team (MDT) outpatient appointment led by medical consultants with extensive experience of working with children diagnosed with OI.

Aims/ Objectives

Following informal feedback from families who received outreach visits through the service, it was hypothesised that outreach visits provided a supportive opportunity for parents to meet and receive advice from various members of a highly specialised OI MDT, to prepare them for practical aspects of caring for their baby.

Method

Five children received one or more outreach visits from a specialist occupational therapist, clinical nurse specialist and/or consultant. At the initial outreach visit, the babies ranged from 10-19 days old. The parents of these babies completed an anonymous questionnaire developed by one of the occupational therapists and clinical nurse specialist within the service. The questionnaire was completed either online or in a paper-format, which consisted of five multiple choice questions and six free text boxes.

Results

Of the five babies, 40% were seen at home, 20% in hospital and 40% at both home and hospital. These visits were attended by an occupational therapist 100% of the time, by a CNS 80% of the time and a medical consultant 20% of the time. 100% of families felt well supported prior to the outreach visit and 100% felt able to ask specific questions during their visit. When asked which topics were helpful to be discussed during the visit, 60% said "what is OI", 80% said "treatment", "items that help manage your baby,



information on the OI service and fracture management”, and 100% said that “practical day to day care of your baby, what happens next and points of contact”. 80% of respondents replied that nothing further would have been helpful to be discussed, with one family suggesting that written information sheets would have been helpful to aid the understanding by the extended family. 100% felt that that the outreach visits were useful and on a 1 – 10 visual analogue scale, where 10 was very likely and 0 was very unlikely, 100% reported they would be very likely to recommend an outreach visit to another family with a new baby presenting with severe OI.

Conclusion

Outreach visits provided a supportive opportunity for parents to meet and receive advice from various members of a highly specialised OI MDT, preparing them for practical aspects of caring for their baby. This supports the need to continue offering this type of service prior to the baby’s first medical MDT appointment. The responses received have demonstrated that practical information alongside general service information is appreciated by the families and supporting centres in the early post natal management of this patient group.

(Poster in next page)

Rita Russo Belo^{*1}, Cristiana Martins¹, António Trindade¹, Nilza Ferreira¹

¹Serviço de Pediatria, Centro Hospitalar de Trás-os-Montes e Alto Douro

Osteogenesis imperfecta in children evaluated in the Pediatrics

Department: case review

Introduction

Osteogenesis imperfecta (OI) is a rare inherited connective tissue disorder mainly characterized by osteopenia, bone fragility and pathologic fractures. The majority of patients present autosomal dominant mutations affecting type I collagen genes COL1A1 and COL1A2, leading to reduced production or formation of abnormal type I collagen, which results in bone fragility and other connective tissue abnormalities, such as progressive deafness and dentinogenesis imperfecta.

Methods

The clinical registries of patients with the diagnosis of osteogenesis imperfecta evaluated in ambulatory consultation in the Pediatrics Department of a level A2 hospital between July 2014 and July 2016 were analyzed.

The aim of this project was to characterize the treatment, follow-up and outcome of the patients.

Results

During this period, seven patients have been evaluated in ambulatory consultation in the Pediatrics Department, with a slight predominance of males (57.1%). The mean age by the time of last consultation was 10.6 years. The majority of patients (71.4%) had undergone prophylactic treatment with pamidronate and those who were treated with



this drug had overall less fractures than those who were not treated (mean number of fractures 3.6 vs 5). After the prophylactic treatment, the mean number of fractures was 1.8. Bone densitometry was performed in three patients (42.9%) and two of the cases had reduced bone density. Three patients had Otorhinolaryngology follow-up consultation and two had Ophthalmology consultation. Five patients (71.4%) were being treated with calcium and/or vitamin D supplements.

Conclusions

Prophylactic treatment with pamidronate is associated with a reduced number of fractures. It is important that patients with OI have an adequate follow-up in order to prevent the consequences of this pathology.

(Poster in the next page)

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*Escola Superior de Tecnologia da Saúde IPL; Faculdade de Psicologia UL

** Faculdade de Psicologia UL

It is a family stressful experience: Pain in children with Osteogenesis Imperfecta

Research has shown that pediatric pain is experienced by all family members and can disrupt family life. Family response to pain, as well as specific parental attitudes, have also been recognized as being important to children's reinforcement of pain behaviors. Osteogenesis Imperfecta (OI) is a chronic congenital medical condition. Most patients with OI experience pain on a daily basis.

Objectives

We aimed to understand how children with OI, their parents and their siblings experience pain. Three domains were studied: the implications of pain on the subject and on his whole family's life; their worries about pain and their ways of coping with the patient child's pain.

Methodology

Seven families of OI children (aged between 5 and 16 years) participated. We used an in-depth semi structured interview; participants' verbatim was audiotaped for further qualitative analysis.

Results

When referring to child's pain or to situations of physical suffering, all family members describe negative feelings of sadness, distress and helplessness. However, despite sharing the same emotions, children, siblings and parents reported different worries. While patients and young siblings focused exclusively on the immediate situation, expressing the urgent need to control the pain and suffering, for parents and older siblings, pain and fractures also activated concerns about the children's vulnerability and the future consequences of OI. Parents also more permissive attitudes towards the child; and family conflicts. Children with OI focus on disability and dysfunction resulting



from pain, and on difficulties in being heard by adults. Siblings consider pain as a sign of disease severity; they also reported the need to protect the patient. Concomitantly, they refer a parental positive discrimination of the sick child. Regarding coping strategies, parents and siblings describe the imposing need to help the child cope with the situation either through distraction or comforting. Other coping strategies emerged namely, avoidance, planning, attribution of meaning and positive reappraisal.

Conclusions

These results can contribute to a better understanding of the experience of the family in one of the most potentially disturbing situation related to OI allowing to tailor health professional's support to these patients and their families

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¹Serviço de Reumatologia; ²Serviço de Pediatria, ³Serviço de Ortopedia. Hospital Garcia de Orta, Almada, Portugal

Osteogenesis Imperfecta: The experience of one single center in Lisbon

Introduction

Osteogenesis imperfecta (OI) is a rare genetic connective tissue disease characterized by bone fragility and osteopenia. Its prevalence is about 1:10000-20000 births. The clinical presentation of OI is extremely variable, including increased susceptibility to fractures, low bone mass, short stature, progressive skeletal deformities, bluish sclera, dentinogenesis imperfecta and hearing loss. In the absence of further curative treatment, treatment goals are the prevention and control of signs and symptoms and promoting the development of bone mass and muscle strength to maximize the capabilities of independent mobility. The treatment is based on three fundamental pillars: medical therapy, with the use of bisphosphonates, orthopedic surgery and rehabilitation.

Methods

Observational, longitudinal, retrospective study based on data obtained from consultation of medical records of all patients with OI followed at Garcia de Orta Hospital in the period between September 1998 and the present. In 1998 it was implemented the treatment protocol for children with OI subsequently revised in 2005, which includes a multidisciplinary approach, regular monitoring (quarterly analytical assessment, annual densitometry, MRI of spine) and therapy with pamidronate and / or oral alendronate. Recently a child was treated with zoledronate. The therapy is continued until obtaining Z-Score within the normal range (-2 a 2) or tolerated in case of no adverse effect.

Results

During this period were followed 26 patients, 72% female with an mean age of diagnosis of 14.9 ± 5.9 years and the current mean age of 21.5 ± 14.4 years. Nineteen had known family history of OI and all had registered the type of OI, classified based on clinical



criteria (17 type I, 5 type IV, 4 type III). Of the 26 patients, 24 started the protocol with bisphosphonates, starting on average at 11.3 ± 11.3 years and mean treatment period of 4.7 ± 2.6 years. The average number of fractures before the treatment was 7.4 ± 5.4 fractures. In all cases it showed an improvement in bone density (average z-score: -4.61 pretreatment, post-treatment -0.69). Of the 24 patients, 18 achieved the desired objectives and stopped therapy; however, 8 patients experienced fractures after therapy. Eleven patients lost follow-up in our hospital, or were transferred to other hospitals. There was 1 death.

Conclusions

OI is a disease with a wide clinical variability which mainly depends on its genetic type. Although there is no curative treatment, medical treatment with bisphosphonates significantly improves the z-scores on bone densitometry of treated patients, revealing an important advance in the treatment of these patients. A deposition of these drugs on bone during very long periods requires more studies with long follow-up to ensure the efficacy and safety of these drugs in the treatment of these children.

(Poster in next page)

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*the authors contributed equally to the work.

Clinical Characterization of a Group of Portuguese Patients with Osteogenesis Imperfecta: a First Report

Introduction

Osteogenesis Imperfecta (OI) is one of the most common genetic diseases of the skeleton, with an estimated incidence of around 1 to 5 cases per 10 000 individuals per year. OI is not restricted to skeleton and a wide range of extra-skeletal manifestations may occur. Given that OI is a rare disease and has a variable phenotype, it may be underdiagnosed by physicians. However, its early diagnosis is essential for an appropriate treatment and follow-up and increased quality of life of patients. OI is genetically heterogeneous, and although the majority of cases are caused by defects in collagen type 1 synthesis and structure (*COL1A1* and *COL1A2*-related OI), an increasing number of other causative genes has been discovered. There is some evidence that the molecular etiology of OI may affect therapeutic response. Thus, a molecular characterization of patients may be important not only for genetic counseling but also from a prognostic and therapeutic point of view. In Portugal, the true incidence of OI is



unknown and a large-scale clinical and molecular characterization was never performed. Furthermore, molecular tests for milder forms of OI are not routinely performed.

A research project coordinated by the Department of Genetics of Centro Hospitalar Lisboa Norte (CHLN), in collaboration with other Portuguese departments of genetics and Hospital Universitario La Paz (Madrid) is ongoing, and aims to clinically and molecularly characterize a large series of Portuguese patients with OI, to establish a comprehensive genotype–phenotype correlation and to assess the management and follow-up differences of OI patients in Portugal. This is a preliminary report of this project with the patients already recruited.

Materials and methods

Our research project consists in a clinical and genetic evaluation of a group of Portuguese patients with confirmed or suspected OI. During a consultation of genetics, a standardized questionnaire containing demographic, orthopedic, imagiologic, therapeutic and follow-up data is applied. Subsequently and after informed consent, a next-generation sequencing (NGS) multigene skeletal dysplasia panel, including among others the known genes associated with bone fragility disorders, is performed at Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz (Madrid). In this preliminary report, we will focus on patients that were evaluated in consultation at Department of Genetics of CHLN and Centro Hospitalar e Universitário de Coimbra during 2 months (July-August, 2016). Molecular characterization of these patients is in progress.

Results

Thirty-one patients (28 families) were included, of which 20 (64.5%) were female and 11 (35.5%) were male. The mean age of the patients was 28.9 years (SD=15.2). No close consanguinity was found between parents of patients. More than one-third of patients never received bisphosphonate therapy. According to Sillence classification of OI, the majority of patients were type I (83.9%), 3 (9.7%) were type IV and 2 (6.5%) were type III.

Among the patients with OI type I, the mean number of fractures was 26.1 (SD=8.1) and the mean age of first fracture was 2.6 years old (SD=3.0). The majority of them (72%) had no limitation of daily living and only 1 (4%) was non-ambulatory. Only 2 patients (7.7%) had prenatal manifestations of OI. Eighteen patients (69.2%) reported visual impairment, 9 (27.5%) reported hearing loss, and 18 (72.0%) had easy bruising. On physical examination, 10 patients (43.5%) had scoliosis, 11 (42,3%) had thorax deformities, and only 1 (3.8%) had *dentinogenesis imperfecta*. Blue sclera was present in 21 patients (80.8%). Most of pediatric patients maintain a regular evaluation by a pediatric orthopedist. Contrarily, the majority of adult patients had not a regular follow-up in orthopedic or rheumatology consultation. Additionally, most of the patients had not a hearing or visual assessment or a regular dental examination.

All the 3 patients with OI type IV reported more than 100 fractures and were non-ambulatory. Only one had blue sclera and none had hearing loss. All of them had thoracic deformities. Two brothers had OI type III, with an autosomal recessive



inheritance suspected. They had facial dimorphisms, and severe limitation of daily living and bone deformities. The two brothers didn't present blue sclera, hearing loss and visual impairment.

Conclusions

This report confirms that OI is a clinically heterogeneous disease. In particular, extra-skeletal problems are variable and common; they require appropriate medical evaluation that should be performed as soon the diagnosis is established. The frequency of fractures is also very variable, and they may be underdiagnosed in some cases. Most patients didn't receive bisphosphonates. Although the effects of bisphosphonates on fracture prevention in mild forms of OI are uncertain, an early diagnosis is essential at least to initiate appropriate orthopedic or rheumatologic follow-up. These aspects support also the idea that OI must be managed by a multidisciplinary and experienced team.

This project is the first large-scale multicentre study analyzing the genotypes and phenotypes of Portuguese patients with OI, and shows the importance of an inter-institutional collaboration to better understand the needs of patients with OI.



Organizers



Abstracts

Pre-Congress Course

(The sessions in this course will be spoken in Portuguese)

Dr Anabela Bandeira

Pediatrics, Unit of Metabolic Diseases, Centro Hospitalar do Porto

Introduction to Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heritable disorder of bone formation resulting in low bone mass and a propensity to fracture. Prevalence is estimated at between 1/10,000 and 1/20,000. The bone fragility has led to the adoption of the trivial name of “brittle bone disease”.

It exhibits a broad range of clinical severity, ranging from multiple fracturing in utero and perinatal deaths to normal adult stature and a low fracture incidence. Other clinical features include the presence of blue sclera, dentinogenesis imperfecta, skin hyperlaxity and joint hypermobility.

OI has been recognised as a disease entity since the 17th century, when it was termed congenital osteomalacia. The term osteogenesis imperfecta was adopted in the late 19th century.

OI is classified into five major subtypes based on genetic, radiographic and clinical presentation. However, it is appreciated that in reality the disorder represents a continuum of severity and that patients do not always fall conveniently into one clinical category. In 1979 Silience proposed a classification of OI into four types based on clinical variability. In 2004, OI type V, VI and VII were added to this classification. In 2004 and 2007 this classification was expanded to types V-VII because of distinct clinical features and/or different causative mutations. At the 2009 meeting of the International Nomenclature group for Constitutional Disorders ICHG of the Skeleton (INCDS) (Published as 2010 Nosology), a decision was made to group the known OI syndromes into five groups. The importance of the different genetic causes of the OI types was acknowledged by encapsulating the causative genes as subtypes of OI types I–V.

Diagnosis is usually clinical. History should include attention to fractures, back pain, motor development and family background. Examination should focus on the skeleton, including the spine, and on identifying other features which support the diagnosis, including scleral hue, teeth and ligamentous laxity. However, there may be few physical findings to support the diagnosis in mild cases. Investigations include serum calcium and vitamin D levels, markers of bone formation (C-terminal propeptide of type I procollagen) and markers of bone resorption (C-telopeptide of type I collagen) and other bone turnover markers: osteocalcine and serum alkaline phosphatase.



Organizers



Radiological studies reveal osteoporosis and the presence of wormian-like bones. Bone densitometry (Dual Energy X-ray Absorptiometry) confirms the low bone mass.

OI is most commonly caused by autosomal dominant mutations in genes coding alpha-1 and alpha-2 chains of type I collagen, indeed mutations in the COL1A1 and COL1A2 genes are responsible for more than 90 percent of all cases of OI. The autosomal recessive forms are caused by mutations in genes encoding proteins involved in posttranslational modification of type I collagen. Various mutations can occur in all the classical forms of osteogenesis imperfecta (types I-IV), but genotype/phenotype correlations are complex and often unpredictable.

Treatment of osteogenesis imperfecta by bisphosphonate therapy can improve bone mass in all types of the disorder, and while not being a cure for the disorder does improve the quality of life of the patient. Cyclic intravenous pamidronate administration reduces bone pain and fracture incidence, and increases bone density and level of ambulation, with minimal side effects. Effects on bone include increase in size of vertebral bodies and thickening of cortical bone. These results allow for more efficacious corrective surgery using intramedullary rodding of the long bones and paravertebral instrumentation.

Specific occupational and physiotherapy programs are integral parts of the treatment protocol as the multidisciplinary approach.

Dr Patrícia Almeida Dias

Serviço de Genética – Hospital de Santa Maria, CHLN E.P.E.

Classification and Genetic Diagnosis

Osteogenesis Imperfecta (OI) designates not a single pathological entity, but a group of inherited connective tissue disorders. Common to all types of OI is the bone fragility that predisposes to spontaneous fractures or fractures associated with minimum trauma. The severity of skeletal disease is very heterogeneous, ranging from lethal to very mild disease with no growth delay or bone deformity. Associated extra-skeletal manifestations are diverse, including progressive hearing loss, blue/ grey sclera and dentinogenesis imperfecta. The first OI classification proposed by Sillence et al in 1979, was based in these clinical features and disease severity. The four types of OI of Sillence classification are very well correlated with defects in collagen type I synthesis (quantitative abnormality) or structure (qualitative abnormality) resulting from pathogenic mutations in *COL1A1* or *COL1A2* genes.

Abnormalities in these two genes present an autosomal dominant inheritance and correspond to about 85%-90% of OI cases. Rauch and Glourieux in 2004, further expanded this classification to seven distinct types, based on clinical features but also in particular radiological aspects (type V), specific histopathological characteristics (type VI) or newly discovered molecular aetiologies (type VII). Since then, the technological advances in massive DNA sequencing, has allowed the discovering of an increasing number of new genes causing rare forms of autosomal recessive types of OI. These new



genes codify for proteins related with collagen type I processing, post-translation modification, folding and crosslinking, but also for proteins involved in molecular defects affecting the bone mineralisation and osteoblast development. The genetic diagnosis of each case of OI is now facilitated by multi-gene panel analysis approach using next generation sequencing technologies. This should allowed the scientific community in collaboration with patients and their physicians, to improve the knowledge of OI by finding genotypephenotype correlations that can result in a better and more effective treatment of each particular case.

Dr Margarida Custódio dos Santos, Luísa Barros, Ana Filipa Pires

Faculdade de Psicologia da Universidade de Lisboa, Escola Superior de Tecnologia da Saúde de Lisboa

The Impact of Diagnoses on Families

Chronic clinical conditions are often very demanding bough for patients and their families. Although the impact of OI is partially determined by its severity type, a large number of OI patients and their families share common challenges that may affect their psychological wellbeing and their quality of life. These challenges are not only health-related but also of emotional, educational, social and financial nature.

Despite consensual recognition that OI treatment should be patient and family centered there is still a lack of knowledge on psychosocial issues that can contribute to tailored effective interventions.

Considering our own clinical experience and research on OI psychosocial issues, this presentation will focus on the most stressful situations lived by patients, parents and siblings of children with OI; on how these situations are lived by all family members; and on their efforts to cope with the situation.

In a qualitative study with 7 Portuguese families (patients; parents and siblings) we used an in-depth semi-structured interview that included open-ended questions about each family members experience on living with OI. Data analysis allowed the identification of similarities and differences concerning the situations that are regarded as most challenging and each participant experiences when living those situations. Fractures and pain; Hospitalization; Home recovery; (re)Entering school; and the time of diagnosis emerged as the most challenging situations. Diverse coping strategies (e.g. distraction, social support; planning, reappraising; avoidance) were identified.

Our findings highlight the dynamic and intrinsic process of adaptation and reinforce that listening to these families can provide important information. The same situations are lived differently according to the subjective experiences and individual challenges faced by each family member. As expected, these challenges differ according to the specific role of each one.

These findings will be discussed and some contributions will be underline to increase better support for this families.

(We Thank APOI for their support)



Organizers



Dr Paula Garcia

Centro de Referência em Doenças Hereditárias do Metabolismo
Centro Hospitalar e Universitário de Coimbra

Medical Treatments in Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder with a broad phenotypic and molecular heterogeneity. Is a rare bone fragility heritable disorder and the most prevalent in children. Mutations in the two genes coding for collagen type I alpha accounts for the majority of individuals, but in the past years, defects in other genes have been associated to OI phenotype.

This syndrome can lead to bone fractures and progressive deformities, including scoliosis. In addition to the skeletal picture, common additional extra skeletal manifestations comprise blue sclera, *dentinogenesis imperfecta*, vascular fragility, and hearing loss.

Multidisciplinary management can improve quality of life and intends to reduce the morbidity associated to fractures, pain, and bone deformities. Disciplines involved should comprehend: physical therapy, medical treatments and orthopedic surgery as necessary, along with optimizing Vitamin D status and calcium intake.

Medical treatments consist mainly in implementing tailored healthy life-styles and bone-remodeling drug therapy. Bisphosphonates are broadly used in the control of moderate to severe *osteogenesis imperfecta*, from infancy to adulthood and appears to be safe. Other more recent drug therapies include teriparatide and denosumab. All these therapies target the symptoms and have effects on the mechanical properties of bone due to modification of bone remodeling, appearing to influence outcome. Therapies, like stem cell transplantation, targeting the specific altered pathway rather than the symptoms, are in development. The safety and efficacy of these new approaches in OI is far from been established.

The focus of this work will be on the existing approved medical therapies. Oral or intravenous bisphosphonates are the most currently used, showing a marked effect on vertebra in growing children and also in vertebral reshaping after compression fractures, but seems to have minor effect on the scoliosis development. Bisphosphonate treatment decreases pain and long-bone fracture rates, influencing the final stature on those that still have potential.

The experience of Coimbra Pediatric Hospital in the last 15 years will be discussed.

Revised OI nomenclature and the pre-and postnatal severity assessment suggested by Sillence in 2014, emphasize the importance of phenotyping in order to diagnose, classify and assess the OI severity, aiming to provide patients with more accurate information into the prognosis of this disorder and allowing physicians to evaluate the effect of implemented therapies.



Organizers



Dr João Lameiras Campagnolo

Surgical Treatments in Osteogenesis Imperfecta

The surgical approach of OI patients has some particular issues. There are some “milestones” to fulfill before a surgical solution: correct diagnosis of the disease, correct diagnosis of the osteo-articular consequences (deformity and/or fracture), awareness of fractures and of medication background and capacity of the surgical team to treat that “unique” patient. These are some essential factors to take in consideration.

In a surgical point of view, the strategies and the techniques employed depend also on several factors: age, size and density of bones, magnitude of deformities, exact location of fractures (articular, non-articular), post-operative conditions (physical therapy, orthoses, day care), disposal of different osteosynthesis adequate solutions (nails, growing rods, hydroxyapatite pins/screws, ...), and adequate surgical team formation.

Surgical treatment OI patients is a challenge. Those patients should probably be treated in orthopaedic reference centers.



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Bios Speakers, Authors and Moderators

(in alphabetical order)

Dr. Andrea Aliverti

Andrea Aliverti received the PhD in Bioengineering in 1997 (Prize Paolo Durst, for the best Italian PhD thesis in Biomedical Engineering) from the Politecnico of Milano University (Polimi), Italy. Currently, he is Professor at the Department Electronics, Information and Bioengineering (DEIB), Polimi, where he teaches Sensors and Instrumentation Technologies and Bioengineering of the Respiratory System. Since 2014, he is the Coordinator of the PhD Programme in Bioengineering at Polimi. His main research interests include the bioengineering of the respiratory system, physiological measurements, biomedical instrumentation and sensors, lung imaging. Responsible of Respiratory Analysis Lab, he has been responsible of Polimi unit in several EU (BREATH, BREATH-PGC, CARED and PLANHAB) and NIH funded Projects. On 2004, he won the ERS (European Respiratory Society) COPD Award. Author of more than 130 papers in peer-reviewed scientific journals, 8 book chapters, editor of 3 books, inventor in 13 patents and author of more than 180 abstracts and brief communications. Member of the editorial board of several scientific journals, he is currently Secretary of the ERS Assembly “Clinical Physiology, Sleep and Pulmonary Circulation”, member of the ERS Educational Council, Chairman of the ERS Task Force ‘Functional evaluation of lung and airways’.

Dr. Jeremy Allgrove

Dr Jeremy Allgrove is Consultant Paediatric Endocrinologist at Great Ormond Street Hospital, UK specialising in metabolic bone disease and disorders of calcium and phosphate.

He qualified from Cambridge University in 1973 and undertook his training in paediatrics and endocrinology in London and Birmingham before becoming a consultant paediatrician in the East End of London in 1988.

His MD Thesis was entitled “Studies of biologically active parathyroid hormone using a cytochemical bioassay with special reference to disorders of calcium metabolism in children.” He is the author of more than sixty scientific papers and now runs the metabolic bone clinic and is a member of the multidisciplinary osteogenesis imperfecta clinic at great Ormond Street Hospital for Children.



Dr Anabela Bandeira

Pediatrics, Unit of Metabolic Diseases, Centro Hospitalar do Porto. Medical doctor licensed by Faculty of Medicine, University of Porto with specialty in Pediatrics and Metabolic Diseases. Research and Training: United Hospital do Porto, Hospital de Santo Antonio. Trained in Metabolic diseases in Hospital de Maria Pia, Porto from January 2007. Trained in Metabolic Diseases in Hospital Robert Debré, Paris in 2007.

María Barbero

Medical and technical translator (Universidad de Salamanca, Spain, Lic. 1985; University of Massachusetts Amherst, PhD ABD 2001). Active in the OI world since 1994. Affiliated to national OI organizations in Germany, Spain and Ecuador. Founder and president of Padrinos-OI/OI-Paten (Germany). Delegate for Padrinos-OI in the OIFE. Responsible for publications and international affairs in Fundación Ahuce (Spain). Community manager of the Spanish speaking OI-List and the Spanish FB OI community. Coordinator of the international Padrinos-OI treatment units.

Prof Luísa Barros

Professora Catedrática da Faculdade de Psicologia da ULisboa. Licenciada e Doutorada em Psicologia; Agregada em Psicologia da Saúde pela Universidade de Lisboa. Leciona disciplinas de Psicologia da Saúde, Psicologia Pediátrica, Psicopatologia da Criança e do Adolescente na Faculdade de Psicologia, e colabora com a Faculdade de Medicina Dentária da ULisboa. Integra a Comissão Científica do Doutoramento em Enfermagem da U.Lisboa. Coordenadora do Grupo Clinical and Health Psychology-Development and Change Processes do CICPsi, Universidade de Lisboa. Publicou vários livros, capítulos e artigos internacionais e nacionais sobre psicologia pediátrica, saúde e desenvolvimento e parentalidade.

Dr Markus Bastir

Markus Bastir (Museo Nacional de Ciencias Naturales, CSIC); Daniel García-Martínez (Museo Nacional de Ciencias Naturales, CSIC); Nicole Torres-Tamayo (Museo Nacional de Ciencias Naturales, CSIC); Juan Alberto Sanchis-Gimeno (Department of Anatomy and Human Embryology, University of Valencia)
Esther Blanco-Perez (Department of Radiology, University Hospital de La Ribera); Susanna Llido-Torrent (Department of Anatomy and Human Embryology, University of Valencia); Federico Mata Escolano (CT and MRI Unit, ERESA); Paul O’Higgins (Hull York Medical School, University of York, UK), Cristina Utrilla (IdiPAZ, Instituto de investigación, Hospital Universitario La Paz, Madrid), Isabel Torres Sánchez (IdiPAZ,



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Instituto de investigación, Hospital Universitario La Paz, Madrid), Francisco García Ríó (IdiPAZ, Instituto de investigación, Hospital Universitario La Paz, Madrid).

My research career has a pronounced European-based international and mobility background. After my MSc studies using 3D morphometrics at the University of Vienna, Austria, I started a European PhD program within the Atapuerca Research Group in Madrid, focussing on craniofacial human evolution and. In 2004, I moved to the University of York, UK, where I specialized in virtual morphology. After that I took over a position as Experienced Researcher in a Marie Curie RTN carrying out research collaborations at several European institutions (MNCN-CSIC, Max Planck Institute for Evolutionary Anthropology, University of Vienna, and University of York, among others). In 2010 I got a permanent research job at the MNCN where I work in the Palaeoanthropology Group. As PI of several research projects I built up the Virtual Morphology Lab-MNCN and trained a lab team with currently associated 3 PhD-researchers, 5 MSc students and one technician.

Prof. Milan Bayer, M.D., Ph.D.

Born 1956 in Prague. 1981 graduated from Charles University, Faculty of Pediatrics. Following education: 1984 Postgraduate specialisation in Pediatrics of I.st degree; 1989 Postgraduate specialisation in Pediatrics of II.nd degree; 1999 Ph.D.; 2011 Postgraduate specialisation in Clinical osteology. Teaching appointments: 1989-1991 Lecturer in Pediatrics; 1991-2002 Senior Lecturer in Pediatrics; 2002-2007 Associate Professor of Pediatrics; 2007 – Professor of Pediatrics. 2008-2015 Head of Dept. of Pediatrics, Charles University, Faculty of Medicine in Hradec Králové. Author of monograph Metabolic skeletal diseases in childhood (2002, 340 p.) Author and coauthor of 21 other monographs and chapters in textbooks; 170 papers in scientific journals. Married, two children.

Dr Atul Bhaskar

FRCS Tr & Orth, FRCS, M.S., M.Ch UK. Paediatric Orthopaedic Surgeon Bombay Hospital Institute of Medical Sciences

Dr Emilia Biffi

Emilia Biffi was born in Bergamo (BG) on 1983. She graduated at Politecnico di Milano in 2007 in Biomedical Engineering and PhD Degree Bioengineering in 2012 with a thesis entitled “Development of innovative devices for reliable studies of in vitro models of Central Nervous System pathologies”.

She is working since 2013 at the Bioengineering laboratory of the Scientific Institute Eugenio Medea in Bosisio Parini (LC) where she is involved in projects on new technologies for rehabilitation and assistance of neuromotor and cognitive impairments of children. She develops and tests medical devices following the European rules,

62



Organizers



manages advanced technologies based on robotics and virtual reality, works with motion analysis systems and electromyography. She is used to work in team with other engineers coming from different backgrounds as well as clinicians and physiotherapists. She authored many publications (h-index = 7), participated in multidisciplinary project meetings and participated in international conferences and workshops. She is the book Editor of a 14-chapter book in the Springer series named “Neuromethods”, entitled “Microfluidic and Compartmentalized Platforms for Neurobiological Research” (2015), about cutting-edge techniques to design, fabricate and use compartmentalized microfluidic devices in the field of Neuroscience. She has been professor in the class “Electronic and Information Bioengineering” since 2013.

Prof Nicholas Bishop

Nick Bishop is an internationally recognised expert in the field of paediatric bone research with a particular focus on EM/early phase studies in osteogenesis imperfecta, steroid-induced or disease-associated osteoporosis and hypophosphatasia, as well as an interest in early life influences on later skeletal health. Professor Bishop is based in Sheffield, at the UK-leading centre for the management of children with bone disease, with over 500 children attending in-patient and out-patient therapy and the lead designated centre for the nationally-commissioned Highly Specialised Severe, Complex and Atypical Osteogenesis Imperfecta Service.

He has over 100 publications, including papers on risedronate therapy in osteogenesis imperfecta (Lancet 2013); enzyme replacement therapy in hypophosphatasia (NEJM 2012, JCEM 2015), a Lancet seminar on Rickets in early 2014 and vitamin D supplementation in pregnancy and neonatal bone mass (Lancet Diabetes and Endocrinology 2016). He is an Associate Director of the newly formed AR-UK Experimental Arthritis Treatment Centre, leading the bone theme, and President of the Academic Paediatric Association of Great Britain and Ireland.

Dr Rosa Bou

Pediatric Rheumatology Unit. Hospital Sant Joan de Déu, Barcelona, Spain

Graduated in Medicine and Surgery (Universitat de Barcelona). Residency in Pediatrics in Hospital de Sabadell, Barcelona. Attending physician in the Pediatric Rheumatology Unit in Hospital Sant Joan de Déu, Barcelona.

Coordinator of the multidisciplinary group in Osteogenesis Imperfecta in Hospital Sant Joan de Déu. Member of the Working Group in pediatric osteoporosis and Osteogenesis Imperfecta of the Pediatric Rheumatology Spanish Society (Sociedad Española de Reumatología Pediátrica –SERPE). Member of the Pediatric Rheumatology European Society and the Pediatric Rheumatology International Trials Organization (PRINTO). Investigator in national and international research projects on osteogenesis imperfecta and other pediatric rheumatology diseases. Publications, books chapters and congress



lectures in areas of pediatric rheumatology (Osteogenesis Imperfecta, Juvenile Idiopathic Arthritis, Uveitis, Kawasaki disease and vasculitis, Autoinflammatory diseases...)

Dr Ana Bueno

Licenciado en Medicina y Cirugía (Universidad de Salamanca). Especialista en Traumatología y Cirugía Ortopédica. Miembro Numerario de la SECOT y del Grupo de Estudio de Traumatología y Ortopedia Infantil. Socio fundador de la Sociedad Española de Traumatología y Ortopedia Infantil y miembro de la Asociación Ponseti de España. Miembro honorífico la FEOI (Ecuador 2011), socia de honor de Ahuce 2012 y Presidenta del Comité Científico de la Fundación AHUCE.

Certificado del Sistema de Calidad ISO 9001:2008 como Coordinadora de La Unidad de Cirugía Ortopédica y Traumatología Infantil del Hospital Universitario de Getafe.

Dr. João Lameiras Campagnolo

Senior Consultant in Orthopaedics – Pediatric Hospital Dona Estefânia - Lisbon. Sub-speciality of Pediatric Orthopaedics.

Dr Alistair Calder

Dr Calder has been a consultant radiologist at Great Ormond Street Hospital since 2006. His subspecialist interests include cardiothoracic CT imaging and the radiology of inherited and metabolic bone disorders. He is radiology committee member of the Skeletal Dysplasia Group for Teaching and Research, and an active member of the International Skeletal Dysplasia Society. He is also Consultant Radiologist for the Great Ormond Street Highly Specialised Osteogenesis Imperfecta service.

Dr Manuel Cassiano Neves

Responsável pela Unidade De Ortopedia Pediátrica e do Adolescente, Hospital CUF Descobertas Lisboa. Presidente eleito da EPOS (European Pediatric Orthopaedic Society) Past- Presidente da EFORT (European Federation of the National Associations of Orthopaedics and Traumatology). Membro honorário da CSOT, SECOT, SOFCOT, SOTA e SPOT (Sociedade Portuguesa de Ortopedia e Traumatologia).

Dr Almairis Castillo

Doctora en Medicina y Cirugía (Universidad Nacional Autónoma de Honduras, UNAH). Postgrado de Ortopedia y Traumatología (UNAH). Especialización en Ortopedia y Traumatología Infantil (Universidad de Chile). Postgrado en Ortopedia y Traumatología



Pediátrica (Universidad Nacional Autónoma de México, UNAM). Shriners Hospital for Children, México D.F. Maestría en Dirección Empresarial con Orientación en Gerencia Hospitalaria; Universidad Tecnológica Centroamericana (UNITEC). Médico Docente de Morfología General y Traumatología; Universidad Tecnológica Centroamericana (UNITEC). Jefe de Sala de Servicio de Ortopedia Pediátrica; Hospital Escuela Universitario (HEU).

Luca Celli

2013 Beginning School of Medicine and Surgery, "Sapienza" University of Rome. He has done since 2014 an internship in Congenital Osteodystrophies Center, Policlinico Umberto I Hospital, "Sapienza" University of Rome.

Dr Mauro Celli

Degree in Medicine and Surgery, "Sapienza" University of Rome. Specialization in Paediatrics, "Sapienza" University of Rome. Doctor of Philosophy in Paediatrics, "Sapienza" University of Rome. Since 2013 Director of Rare Diseases and Tumors, Policlinico Umberto I, Rome. 2013 Chief of Congenital Osteodystrophies and Bone Metabolism Center, Pediatric Department "Sapienza". Professor in osteoporosis and skeletal disorders in "Sapienza" University, School of Medicine and Nursing. He is author of many international scientific publications and has constantly participated to conferences about skeletal diseases and bone metabolism.

Dr Nuno Craveiro Lopes

Senior Consultant of Orthopedics and Traumatology since 1992. Head of Orthopaedic and Traumatology Department, Garcia de Orta Hospital, Almada, Portugal since 1991. Hospital Management Graduation, 1994. Fellowship in Paediatric Orthopaedics, Saint Justine University Hospital, Montreal, Canada, 1987. Training Courses on Ilizarov Techniques at Kurgan, 1993 and 1996. Experimental and clinical research on Legg-Calvé-Perthes disease since 1985. 384 presented papers on national and international events. 70 published papers on national and international medical journals. Awards: Dr. Jorge Mineiro SPOT 1986, Dr. Arnaldo Rodo SPOT 1988, Dr. Lino Ferreira HMP 1989. Best Poster SICOT 1999, Best Paper SPOT 1999 and Special Award of the SPOT Medical Journal 2012. President of 8 meetings, 1 sports medicine symposium, 1 international congress and 3 workshops. Redactor of the Portuguese Journal of Orthopedics and Traumatology, 1995-1996. Member of ASAMI International since 1985, SEOI-SPOT since 1990, SEBAL-SPOT since 1996, SICOT since 1993, EPOS since 1996, ISOST since 1997, AAOS since 2000 and ILLRS since 2012. Vice-President of ASAMI-LB 1993-1994 and President 1995-1996. President of SEBAL-SPOT 1996-1998, 2006-2008 and Board Member from 1999 to date. Board Member of SPOT and ISOST since 1999. President of



ASAMI International, 2010-2011 (Association for the Study and Application of the Method of Ilizarov). President of ILLRS 2012-2015 (International Limb Lengthening and Reconstruction Society). President of ILLRS and ASAMI Int 2016-2017. Visiting Professor at São Paulo Federal University, Escola Paulista de Medicina, Brazil, 1996. Visiting Professor at Deemed University, Sri Ramachandra Medical College And Research Institute, Madras, India, 2005. Visiting Professor at Dep. of Orthopaedic, Central Hospital, Skövde, Sweden, 2009 and 2010. Visiting Professor at Dep of Orthopaedic, Graduate School of Medical Science, Kanazawa University, Japan, 2011. Visiting Professor at the Center of Excellence for Hip Diseases, Texas Scottish Rite Hospital, Dallas USA, 2014. Assistant of Orthopedic and Trauma at the Department of Biomedical and Medicine Sciences of Algarve University since 2010. Jury member of thesis in Mechanical Engineering, Faculty of Science and Technology, Universidade Nova de Lisboa, 2015. Jury member of thesis in Medicine and Surgery, Murcia University, Spain, 2016.

Dr Belinda Crowe

Dr Belinda Crowe trained at Queen's University Belfast, completing her general paediatric training at the Royal Belfast Hospital for Sick Children. She relocated to London to undertake subspecialty training in paediatric neurodisability, joining Great Ormond Street Hospital for Children NHS Foundation Trust as trainee in 2013. She was appointed as a consultant with special interest in movement disorders and osteogenesis imperfecta upon completion of training in September 2015. Belinda feels truly passionate about optimising participation and achieving best possible quality of life for children with disabilities and their families. She is delighted to work as part of a multidisciplinary team providing a national Highly Specialised Service for children and young people with OI.

Dr Margarida Custódio dos Santos

Faculdade de Psicologia da Universidade de Lisboa. Escola Superior de Tecnologia da Saúde de Lisboa. PhD in Psychology - Health Psychology. Coordinator Professor in the School of Health and Technology of the Polytechnic Institute, Lisbon (ESTeSL; Invited Professor in the Psychology Faculty of the University of Lisbon (FPUL).

Research and publications in the area of pediatric chronic illness; parenting; children and adolescents health behaviors; health communication. Psychologist at the Community Service of the Psychology Faculty. Psychologist and President of the General Assembly of APOI (Osteogenesis Imperfecta Portuguese Association).



Mariapia de Bari

Mariapia de Bari is physiotherapist since 2002 and starts to collaborate with numerous clinics enriching her experience in the rehabilitative treatment of neurological and orthopedic diseases in children and adults. In 2003 she starts the collaboration with the Congenital Osteodystrophy medical team of Umberto I Hospital (Rome) and the Italian Association of Osteogenesis Imperfecta (ASITOI), and begin her study on Osteogenesis Imperfecta (OI). Between 2002 and 2008 she takes courses in the treatment of children and newborn affected with neurological and orthopedic diseases and participates to National and International Conferences on OI as speaker and poster presenter. The collaboration with the Umberto I Hospital medical team consolidates thanks to the institution of the Rare Diseases Centre and she specializes in the treatment of children with OI and other connective tissue pathologies as Fibrous Dysplasia and Ehlers-Danlos Syndrome. In 2015 Mariapia attains the Osteopathy Diploma getting the principles of global treatment and a high specialization in the treatment of dysmorphisms and traumas in pediatric area. Today she works in the Adults and Children Dysmorphisms Rehabilitative Unit of Vaclav Vojta Centre (Rome) and is Osteopathy Tutor Trainees and Teacher Assistant; she continues to study and update, nourishing the passion for her job.

Dr Joaquín de Nova

Associate Professor on Paediatric Dentistry (Dentistry Degree). Director of Postgraduate Degree (UCM): Integrated Specialist dental care in children with special needs. Associate Professor in the MSc Paediatric Dentistry.

Investigador principal del Proyecto de Investigación: “Estudio del desarrollo craneofacial, unión craneocervical y dental y sus alteraciones, en niños con Osteogénesis Imperfecta tratados con bisfosfonatos”. Fundación Mutua Madrileña (2013). Dirección de 16 Tesis Doctorales (1 en el ámbito de la OI: “La unión craneocervical en el paciente con OI”). Tutor de 5 Trabajos de Investigación fin de Master en CC Odontológicas relacionados con la Osteogénesis Imperfecta.

Socio de Honor de AHUCE. Miembro del comité científico de la Fundación AHUCE.

Dr Patrizia D’Eufemia

1972 Degree in Medicine and Surgery, “Sapienza” University of Rome; 1975 Specialization in Paediatrics, “Sapienza” University of Rome; 1979 Specialization in Infectious Diseases, “Sapienza” University of Rome; 1980 Internship in Department of metabolic disease, Institute of Child Health, London University. 1980-2013 Assistant professor Full time Medical Supervisor at the Department of Pediatrics, “Sapienza” University of Rome Pediatrics and Congenital Osteodystrophies. 2013 retirement. She is author of many international scientific publications and books in skeletal disease and bone metabolism



Dr Catherine DeVile

Dr Catherine DeVile qualified as a doctor in 1986, training at Cambridge University and King's College Hospital, London. She then trained in Paediatrics and subspecialised in Paediatric Neurology and is currently Consultant Paediatric Neurologist at Great Ormond Street Hospital for Children NHS Foundation Trust, appointed as a Consultant in 2000. Her post comprises of a combination of childhood neurodisability and acute child neurology. She is Lead for the Osteogenesis Imperfecta Service at Great Ormond Street Hospital which is one of four nationally commissioned Highly Specialised centres in England for children with severe, complex and atypical OI.

Dr. Patrícia Dias

Serviço de Genética – Hospital de Santa Maria, CHLN E.P.E.

2002, Licenciatura em Medicina pela Faculdade de Ciências Médicas da Universidade Nova de Lisboa. 2004, Conclusão do Internato Geral no Hospital de Santa Marta. 2005, Início do Internato Complementar em Medicina Geral e Familiar no Centro de Saúde de Loures (frequência de 2 anos, não concluído). 2007, Início do Internato Complementar de Genética Médica no Serviço de Genética do Hospital de Santa Maria. 2012, Conclusão do Internato Complementar de Genética Médica. 2013, Assistente Hospitalar de Genética Médica no Hospital de Santa Maria/ CHLN

Kirsten Donnelly

Kirsten Donnelly trained at the University of Sydney, Australia obtaining a Bachelor of Applied Science (Occupational Therapy) in 2009. Upon graduating, Kirsten has specialised in paediatrics in a range of settings including acute hospital, community and special schools in Sydney, Australia. Kirsten moved to London in 2014, where she commenced work at Great Ormond Street Hospital for Children. Whilst working with children who underwent complex orthopaedic and spinal surgery, Kirsten developed an interest in Osteogenesis Imperfecta (OI) and child development. Kirsten joined the highly specialised OI and neurodisability service, as a senior occupational therapist, and continues to work in areas of special interest such as early development of children with OI and the new born baby outreach service. She is passionate about improving the lives of children with OI and their families. Through her work, she aims to increase their participation in every day activities in environments such as home and school.

Karen Edwards

Karen Edwards is a Clinical Specialist Physiotherapist and has worked at Great Ormond Street Hospital for seven years.



Karen graduated from The Prince of Wales School of Physiotherapy in 1986 with a Diploma in Physiotherapy. Post qualification she joined the physiotherapy team at Colchester General Hospital, working in acute paediatrics for 2 years. In 1989 Karen moved to London and specialised in Community Paediatrics where she worked for 20 years before joining the Movement Disorder Service and Botulinum Toxin Service at Great Ormond Street Hospital in 2009. She joined the Highly Specialised OI Service at Great Ormond Street Hospital in 2011 and has a specialist interest in the gross motor development of children with OI. She has a particular interest in the orthotic management of these children. In 2004 her MSc dissertation study used motion analysis to investigate whether wearing Lycra garments changed posture and movement in children with cerebral palsy. During her career Karen has also worked part-time with groups of other health professionals to improve clinical education and continuing professional development. Karen regularly presents at National Conferences on Movement Disorders and also Continuing Professional Development.

Dr Carolina Escalda

Licenciatura em Medicina pela Faculdade de Medicina de Lisboa-1985.
Mestranda em Engenharia da Saúde pela Faculdade de Engenharia da Universidade Católica Portuguesa-2003. Chefe de Serviço de Ortopedia e Traumatologia do Hospital Garcia de Orta, Almada - 2006.
Diretora do Serviço de Ortopedia e Traumatologia do Hospital Garcia de Orta, Almada – 2016.

Alessandra Febbo

2016 Degree in Medicine and Surgery, "Sapienza" University of Rome. 2016 Beginning Specialization in Paediatrics, "Sapienza" University of Rome. She has working since 2015 in Congenital Osteodystrophies Center, Policlinico Umberto I Hospital, "Sapienza" University of Rome.

Tamara Fernández Juan

Degree in Psychology. Master Degree in Counselling. Expert in psychosocial intervention in crisis, emergencies and disasters.
Psychologist at the Spanish Osteogenesis Imperfecta Association (AHUCE) since 2013. Broad experience in counselling and psychological intervention with people with OI and their families. Guidance and specific training about OI to patients, professionals and general population.



Dr Nilza Ferreira

Pediatrician in Centro Hospitalar de Trás-os-Montes e Alto Douro. Degree in Medicine by Faculty of Medicine of University of Porto, Portugal, in 1978. General Residency in Hospital Geral de Santo António, Portugal, 1980. Peripheral Medical Service in Madeira, Portugal, in 1981. Pediatrics Residency in Hospital Geral de Santo António, Portugal, between 1983 and 1988.

Dr Paolo Frascini

Born in Milan on 06.30.1954. Graduated 8.6. '80 In Medicine and Surgery and in Physical Therapy and Rehabilitation in 1983 at the University of Milan. MD specialist in rehabilitation since 1986 In Rehabilitation Unit of the Scientific Institute "E. Medea" in Bosisio Parini (LC). Since the Academic Year 2001-2002 is Professor of the Specialization Course in Physical Medicine and Rehabilitation of the University of Milan. Since 1987 he works as a physiatrist with the Italian Association of Osteogenesis Imperfecta and is a member of the scientific group of ASITOI with cooperation with French and Canadian centers of reference for clinical and research activities. Medical consultant for rehabilitation in *OI* in Pediatric Unit Of Verona and Genetic Department of Rizzoli Hospital in Bologna.

He is Italian representative for the WeeFIM scale since 1998, according to a research agreement with the University of Buffalo-U.S.A. National Researcher on Rehabilitation projects in osteogenesis imperfecta.

Last activities: "Induction of osteoblastic activity in vitro and in vivo of subjects with osteogenesis imperfecta with complex fractures or pseudoarthrosis through the use of support matrices based on PCL and hyaluronic acid. " "Italian Network for Skeletal Displasya" (2008-2011). Project Manager of Diagnostic Protocols Therapeutic care for Osteogenesis Imperfecta for Lombardy Region (2011-2012).

Dr Paula Garcia

Paediatrician exclusive in the inherited metabolic diseases field in Coimbra Pediatric Hospital from Coimbra Central and University Hospital. Coordinator of the inter hospitals network of Portugal Centro Region for inherited metabolic diseases. Consulter degree from the Portuguese Medical Doctors College. Active member of the National Coordinator Committee for the Treatment of Lissosomal Storage Diseases.

Prof. Francis Glorieux

Dr Francis H. Glorieux received his MD from the University of Louvain and his PhD from McGill University. It is there that he developed his interest in heritable pediatric bone diseases. His doctoral thesis demonstrated that calcitriol and phosphate allowed for control of the bone disease in hypophosphatemic rickets. This regimen is still used



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worldwide in such patients. He also demonstrated the beneficial effects of bisphosphonate in severe forms of Osteogenesis Imperfecta. Programs based on the Montreal protocols are now used all over the world. From 1973 to 2011, he was the Head of the Genetics Unit at the Montreal Shriners Hospital for Children and a Professor at McGill University. He is now Emeritus Director of Research at the Shriners Hospital and Emeritus Professor of Surgery, Pediatrics and Human Genetics at McGill. Since 2009, he has been the Chair of the Medical Advisory Council of the Osteogenesis Imperfecta Foundation (USA). He has published more than 290 peer-reviewed papers, and co-edited 3 books. He is the recipient of both the Bartter and the Neuman Awards of the American Society for Bone and Mineral Research (ASBMR). He holds honorary doctoral degrees from the Universities of Amiens and Lyons (France). In 2004, Dr Glorieux was made an Officer of the Order of Canada, the country's highest honor for lifetime achievement.

Dr Fátima Godinho

Rheumatology Specialist at Hospital Garcia de Orta, Almada since 2005. Senior Rheumatologist Consultant since 2015. Vice Presidente of the Portuguese Association of Osteogenesis Imperfecta. Member of the Portuguese Society of Rheumatology and member of the Rheumatoid Arthritis Study Group and the Spondylarthropathies Study group. Medical Assistant of the National Association of Ankylosing Spondylitis. Key responsibilities: Conducting patients follow-up in inpatient; Outpatient clinics and Rheumatology Day Care Unit; Held responsibility in Rheumatology; Conducting clinical trials in Inflammatory Rheumatic diseases. Author or/and co-author in several scientific publications in national and international journals in the Rheumatology field. Active Participation in several congress, courses, symposium and patients meetings in the Rheumatology field.

Dr Pilar Gutiérrez

Bachelor in Medicine and Surgery (Universidad Complutense de Madrid). Specialist in Pediatrics. Degree of Research Capacity on Legal and Forensic Medicine. Head of the Pediatrics Section (Hospital Universitario de Getafe) until 2015. Long experience in Pediatric Endocrinology, Child Abuse and Osteogenesis Imperfecta. Since 2000 in charge of monitoring and treatment of OI patients in a multidisciplinary team. Leader in Spain in Bisphosphonates and Denosumab use in OI.

Professor of the teaching unit of the Cruz Roja Española de la Escuela Universitaria de Enfermería (Universidad Complutense de Madrid). Professor at the Universidad Alfonso X el Sabio. Associate Professor for Child Endocrinology at the Universidad Europea de Madrid. Honorary member of Ahuce (Spanish OI association) and Vice-President of the Scientific Committee of the Fundación Ahuce.



Mark Heathfield

Mark Heathfield trained at Keele University between 2003 and 2006, obtaining a DipHE (Child) Diploma in Children's Nursing. Upon graduation in 2006 he specialised in the care of children and young people with complex orthopaedic and spinal conditions, including Osteogenesis Imperfecta (OI). Whilst working on Great Ormond Street Hospital's orthopaedic and spinal ward in London, Mark gained experience in the management of children with complex orthopaedic, spinal, ophthalmology and General surgical patients. In 2011 he was appointed as Charge Nurse at The Portland Hospital, tasked with helping to set up the Neurorehabilitation service for children. In 2014 Mark joined the OI team at Great Ormond Street Hospital as a Clinical Nurse Specialist. He has particular interests in the new born baby outreach service, orthopaedic management and treatment options for Children with OI, including bisphosphonate treatment. Mark gained a Bsc (hons) in Paediatric Neurosciences, in 2015. Mark was born in Scotland, grew up in Cardiff, South Wales and now lives in Milton Keynes.

Dr Gaurav Jain

Senior Resident, Bombay Hospital Institute of Medical Sciences.

Antonella Lo Mauro

Antonella Lo Mauro received the Master's degree in Bioengineering in 2012 from the Politecnico of Milano University, Italy. Currently, she is a scientific laboratory technician at the Respiratory Analysis Laboratory of the Department Electronics, Information and Bioengineering (DEIB), Politecnico of Milano University. She is a laboratory teaching assistant for the degree course: Bioengineering of the Respiratory System, Master in Biomedical Engineering, at Politecnico di Milano University. She also teaches at the Master for Respiratory Rehabilitation at University of Milan. Author of 28 papers in peer-reviewed scientific journals, of abstracts and brief communications in different research interests: chest wall kinematics, respiratory muscles action and cardiopulmonary interaction during exercise, respiratory maneuvers and mechanical ventilation in healthy and disease (chronic obstructive pulmonary disease, neuromuscular disease, osteogenesis imperfecta, anesthesia, lung transplantation and thoracic surgery). She collaborates with several hospitals and research centers in Italy and Europe. She was also involved in several EU (BREATH, CARED and PLANHAB) funded Projects.

Dr Jana Lochmanova

Jana Lochmanova, M.D., born 1987 in Cadca. 2013 graduated from Charles University, Third Faculty of Medicine. From 2013 employed at the Department of Pediatrics at the Budweis hospital and enrolled in postgraduate specialisation programme for pediatricians.



Dr Valentina Lodato

2011 Degree in Medicine and Surgery, "Sapienza" University of Rome. 2016 Beginning of Specialization in Genetics. She has worked since 2006 in Congenital Osteodystrophies Center, Policlinico Umberto I Hospital, "Sapienza" University of Rome. She is author of several international scientific publications in skeletal disease and bone metabolism.

Dr Lorena Martini

2001-2007, Degree in Medicine and Surgery, "Sapienza" University of Rome. 2008-2013, Specialization in Orthopaedic Surgery, "Sapienza" University of Rome. 2014, Assistant Medical Director in Department of Orthopaedic Disease, "Sapienza" University of Rome. She is specialized in pediatric orthopaedic surgery and since 2007 he made study research and clinical and surgical assistance to patients affected by rare disease, especially Osteogenesis Imperfecta, rare disease centre in Policlinico Umberto I hospital, "Sapienza" University of Rome.

Dr Cristiana Martins

Third year resident in Pediatrics in Centro Hospitalar de Trás-os-Montes e Alto Douro, Portugal. Master in Medicine by Faculty of Medicine of University of Lisbon, Portugal, in 2012. Common Year Residency in Centro Hospitalar de S. João, Portugal, in 2013. Internship in the Department of Cardiology in Centre Hospitalier de Rambouillet, France, in September 2011. Internship in the Department of Medicine in Unidade Local de Saúde de Matosinhos, Portugal, in August 2011. Internship in the Department of Pediatrics in Centro Hospitalar de S. João, Portugal, in August 2010. Internship in the Department of Pediatrics in Unidade Local de Saúde do Nordeste, Portugal, in August 2009.

Rubén Muñoz

Psychology at the University of Valencia in 2009. In 2013 he completed a Master degree in Clinical Psychology at the Behavior Therapy Center of Valencia and currently studies a Master in Neuropsychology at Universitat Oberta de Catalunya. He has worked in mental health centers, private clinics, family meeting points and since 2015 he works for AHUCE association and also carries out volunteer works at AHUCE foundation. His work aims to improve the quality of life of people affected by osteogenesis imperfecta through individual psychological therapy, workshops, hospital accompaniment and implementation of projects of psychological interest, such as self-help groups.



Dr Amaka Offiah

Dr Amaka C Offiah is Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Radiologist at the University of Sheffield and Sheffield Children's Hospital NHS Foundation Trust. She has particular interest in inherited disorders of the skeleton and physical abuse. Her PhD thesis was on the optimization of imaging methods for suspected physical abuse in children and she has provided expert opinion to Her Majesty's courts in over 200 cases of suspected abuse in children. Dr Offiah has published over 70 papers, books and book chapters (including a Radiological Atlas of Child Abuse) and given more than 120 invited national and international lectures. She is a member of the panel tasked with updating the RCR/RCPCCH Guidelines on Imaging in Suspected Child Abuse and as Chairperson of the European Society of Pediatric Radiology Child Abuse Taskforce was instrumental in the RCR/RCPCCH Guidelines being adopted as the standard for imaging in suspected child abuse throughout Europe. Dr Offiah is the only actively employed UK radiologist on the Board of the European Skeletal Dysplasia Network, Convener of the Skeletal Dyplasia Group for Teaching and Research, Vice Chair of the Yorkshire and Humber (Sheffield) Research Ethics Committee, a standing member of the NICE Guidelines Update Committee and was the RCR 2013 Roentgen Professor – being the first female and the first paediatric radiologist to receive this award.

Dr José Ignacio Parra

Especialista en Traumatología y Cirugía Ortopédica. H.U. de Getafe. Madrid. España.

Dr Pietro Persiani

1990-1996, Degree in Medicine and Surgery, "Sapienza" University of Rome. 1997-2002, Specialization in Orthopaedic Surgery, "Sapienza" University of Rome. 2003-2006, Doctor of Philosophy in Department of Orthopaedic Disease, "Sapienza" University of Rome. 2007, Researcher in Department of Orthopaedic Disease, "Sapienza" University of Rome. He is specialized in pediatric orthopaedic surgery and since 2000 he made study research and clinical and surgical assistance to patients affected by rare disease, especially Osteogenesis Imperfecta, rare disease centre in Policlinico Umberto I Hospital, "Sapienza" University of Rome.

Sara Piccione

Sara Piccione became physiotherapist in 2000 and hydrotherapist in 2001. She started to work as freelance in orthopedic rehabilitation clinics and as home physiotherapist rehabilitating bedridden patients with severe pathologies. During her professional path she took courses in manual therapies and vascular techniques. Since



2003 she collaborates as teacher in hydrotherapy courses with The National Association of Hydrotherapist (ANIK). In 2006 she took part of the organic staff of the Rehabilitation Centre Vaclav Vojta (Rome) where depth her knowledge in vascular and oncologic rehabilitation and began working with neurological patients. In 2009 she started the osteopathy school and in 2010 she entered the Osteogenesis Imperfecta (OI) and Dysmorphism Children Rehabilitative Team of Vojta Centre. Her interesting in OI grew up so that in 2012 she started her collaboration with The Rare Diseases Centre (Umberto I Hospital – Rome) and with The Italian Association of Osteogenesis Imperfecta (ASITOI) participating as specialist in the treatment of OI in national conferences and as author in some international congress poster sessions. In 2015 she became osteopath. Today Sara works in Vojta Centre and is trainees tutor and teacher assistant in osteopathy. She continues updating her professionalism and work with OI people with passion and humanity.

Dr Márcia Rodrigues

Márcia Rodrigues is a Portuguese resident in Medical Genetics (5th year), at the Department of Medical Genetics of Hospital de Dona Estefânia – Centro Hospitalar de Lisboa Central, EPE (Lisboa, Portugal). She has initiated her residency in Medical Genetics in 2009, after working for one year at Hospital de Faro. She took an absence of leave for 2 years (September 2012 to September 2014) to serve as a volunteer for the Portuguese NGO *Leigos para o Desenvolvimento* in Angola and Mozambique, and currently is about to finish the residency program. Her main fields of interest are dysmorphology, skeletal dysplasias, ocular genetics and intellectual disability and other disorders of development.

Dr Clara I. Rodríguez

BioCruces Health Research Institute, Spain.

Dr Clara I. Rodríguez obtained her Ph.D. in 1999 at the Universidad Autonoma de Madrid and the Centro de Biología Molecular Severo Ochoa under the supervision of Prof. Manuel Fresno Escudero, working on parasite activation of the immune system. She next did a short one year postdoc in the same center in Dr Maria Luisa Salas' Lab specializing on viral signaling. In 2000 she moved to the National Cancer Institute at Frederick (NIH; USA) for postdoctoral training in genetic manipulation in mammals. It was during those five years at the NCI where she was introduced and gained experience working on pluripotent stem cells. Dr Rodríguez returned to Spain as researcher at the Valencia Stem Cell Bank (Centro de Investigacion Principe Felipe). In 2006 she moved to the Hospital de Cruces (Bilbao) where she was awarded an investigator contract under the Miguel Servet program to start a new research group focused on stem cell based therapy. Currently, she is Group Leader of the Stem Cells and Cell therapy Laboratory at the BioCruces Health Research Institute, interested in the potential of human stem cells



for the study of human disease and the design of new therapies. She is the Principal Investigator of a national, independent, multicenter clinical trial of cell therapy applied to pediatric patients suffering from Osteogenesis Imperfecta.



Organizers



Miguel Rodríguez

Physiotherapist. Alcala University. (Madrid). Physiotherapist of AHUCE. Physiotherapist for FAD and Adecco. Master neurological physiotherapy and neuromotor control. Rey Juan Carlos University (Madrid) Expert in Bobath Concept. Rey Juan Carlos University and UAX. (Madrid). Expert in cerebral palsy Le Metayer concept. Autonoma University. (Madrid).

Dr Rita Russo Belo

Second year resident in Pediatrics in Centro Hospitalar de Trás-os-Montes e Alto Douro, Portugal. Master in Medicine by Faculty of Medicine of University of Porto, Portugal, in 2013. Common Year Residency in Centro Hospitalar de Trás-os-Montes e Alto Douro in 2014. Internship in the Department of Orthopedics in Bispebjerg Hospital, Denmark, in September 2014.

Dr Belén Sagastizábal

Licenciado en Medicina y Cirugía Formación como Médico Interno Residente en Pediatría y sus áreas específicas en el H. Universitario de Getafe (Mayo 2011 - Mayo 2015). Formación específica en Endocrinología Infantil según el programa de formación de la Sociedad Española de Endocrinología Pediátrica. Profesor colaborador Pediatría Universidad Europea de Madrid. Miembro numerario de la Asociación Española de Pediatría

Dr Ricardo Sanz

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Dr Elena Sevillano

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Dr Suken A. Shah

Division Chief, Spine and Scoliosis Center, Clinical Fellowship Director, and pediatric orthopaedic surgeon at the Nemours/Alfred I. duPont Hospital for Children in



Wilmington, DE. He also serves as Associate Professor of Orthopaedic Surgery and Pediatrics at Thomas Jefferson University in Philadelphia, PA. Dr Shah is certified by the American Board of Orthopaedic Surgery.

Dr Shah earned his medical degree as a *cum laude* graduate of Jefferson Medical College of Thomas Jefferson University in Philadelphia. He completed a surgical internship at The Pennsylvania Hospital and orthopaedic surgery residency training at Thomas Jefferson University Hospital / Rothman Institute in Philadelphia. He received advanced training in pediatric orthopaedics and scoliosis surgery with completion of a fellowship at the Alfred I. duPont Hospital for Children. Dr Shah's academic honors include membership in the Alpha Omega Alpha Honor Medical Society and awards for his research, which he has presented at numerous scientific conferences. Distinctions include a Scoliosis Research Society Traveling Fellowship, Spinal Deformity Education Group Advancement Award, and *Best Doctors in America* (2007-2011). Dr Shah is an active member of national specialty societies and serves on the Board of Directors of the Scoliosis Research Society, chairs the Growing Spine Committee, and is the chair-elect of the Program Committee. He is a member of the Pediatric Orthopaedic Society of North America and multiple research study groups. In addition, he has over 45 research publications in peer-reviewed journals, written 17 book chapters and most recently was a section editor of *Orthopaedic Knowledge Update – 9*, published by the American Academy of Orthopaedic Surgeons. He also serves as a reviewer for four medical journals.

Dr Shah's clinical interests include adolescent idiopathic scoliosis, early onset scoliosis, complex spinal deformities, kyphosis, spondylolisthesis and other problems of the spine, minimally invasive techniques for surgery and cerebral palsy. He is an innovator, researcher and key opinion leader in the field of spinal deformity surgery and performs advanced deformity correction techniques. He trains residents, fellows, and visiting observers in these techniques at the Alfred I. DuPont Hospital for Children. He is frequently invited to teach and lecture at national and international courses, educational symposia, and other institutions.

Dr António Trindade

Pediatrician in Centro Hospitalar de Trás-os-Montes e Alto Douro. Degree in Medicine by Institute of Biomedical Sciences of University of Porto, Portugal, in 1985. General Residency in Centro Hospitalar do Vale do Sousa, Portugal, between 1986 and 1988. Pediatrics Residency in Hospital Geral de Santo António, Portugal, between 1989 and 1994.

Dr Arianna Turchetti

2003 Degree in Medicine and Surgery, "Sapienza" University of Rome. 2014, Specialization in Pediatrics, "Sapienza" University of Rome. She has worked since 2014 in



Organizers



Congenital Osteodystrophies Center, Policlinico Umberto I Hospital, "Sapienza" University of Rome. She is author of several international scientific publications in Paediatrics

Ute Wallentin

Founding member of German OI association DGOI; since 1993 German delegate of the OIFE; OIFE president 2001 – 2015; since September 2015, German OIFE delegate and responsible for "social and networking activities" of the OIFE in close cooperation with its EC

Ingunn Westerheim

OIFE president. Ingunn Westerheim is a legal advisor by education and is currently serving as the president of Osteogenesis Imperfecta Federation Europe (OIFE). The umbrella association consists of organisations which, in one way or another, support people living with Osteogenesis Imperfecta (OI). The goals of the OIFE are:

- Representation of its members on a European level – for example as a member of the European umbrella organisation for Rare disorders „EURORDIS“;
- Presentation of problems and needs of people with OI to national and international organisations, with the aim to have them included in public health programs;
- Networking between professional OI-specialists and treatment centres, national OI associations and OI patients worldwide;
- Promotion of research on all aspects of OI – in cooperation with an international OI-registry based in the US;
- Collection, exchange and publication of information about OI;
- Support of member-societies by the exchange of information and experience
- Promotion of public awareness of OI;
- Support of people with OI in countries without an existing OI society and help to establish an OI association there.

Dr Anna Zambrano

Degree in Medicine and Surgery, "Sapienza" University of Rome. Specialization in Pediatrics, "Sapienza" University of Rome. 2015 Doctor of Philosophy in Biotechnology, "Sapienza" University of Rome. She is specialized in congenital osteodystrophies and bone metabolism diseases since 2002 she made study research and clinical assistance to patients affected by rare diseases, especially Osteogenesis Imperfecta in Rare Diseases Center, Policlinico Umberto I Hospital, "Sapienza" University of Rome.

She is author of many international scientific publications and has constantly participated to conferences about Skeletal Diseases and bone metabolism.





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