Celebrations of our moving process to Belgium coming to an end!

Editorial
By Ingunn Westerheim, OIFE President

In Norway, one of the most famous court cases is called the Rødseth-case. In 1981 a 19-year-old father was accused of child abuse and causing his baby girl’s death. He was sentenced to 2,5 years in prison because his five months old daughter had bruises and a fractured leg. The Supreme Court reduced the sentence to one year and nine months. But after he was released, he claimed he was forced to confess and that his baby was probably suffering from a rare bone condition. He got a lot of support from different people, including one of the most famous female actors in Norway (Wenche Foss). After a change in the criminal law, his case was reopened. Eventually Sveinung Rødseth was completely acquitted, 19 years after he was sentenced to prison for killing his baby girl Therese.

This case was of course for many years a big thing in the Norwegian OI-organization (NFOI), that was established in 1979. But since I was only a toddler when this happened, I don’t really know how the Board was dealing with it at the time. But a feeling got stuck in me, that there is always a (higher) risk that parents of children with OI can be wrongly accused of child abuse.

And then many years later I had a new epiphany. At the scientific OI-conference in Ghent in 2008 I was listening to a radiologist talking about how to differentiate OI and child abuse. And before this, I didn’t really give much thought to the other perspective. But she said it loud and clear: “Don’t forget that children with OI can also be abused!” This really stuck with me.
Since 2001 had been the chair of the Norwegian OI-organization. And I must admit, I was really in doubt of how to handle cases where parents contacted the organization for assistance, after being accused of child abuse. How deeply should the organization get involved? Which side should we support? Which doctors should we refer to? Should we provide information about the process or do more? I think many Board members of OI-organizations around the world have struggled with the same questions during the years.

One thing NFOI did was to contact the professional organization of the pediatric radiologist. Together we developed a course about OI and how to differentiate OI from child abuse. I have no idea if it prevented any court cases, but at least it’s something concrete that the organization can help with.

Earlier this year, we were contacted by Dr Gerard Pals from the Netherlands. He was worried that because of deprecated information about OI and genetics at the organizations’ webpages (incl. OIFE), we could risk that children who had OI didn’t get a correct diagnosis. This could lead to the child being taken from the parents. He encouraged us to create more awareness about the topic and perhaps to educate both professionals and OI-organizations what we should look for and think about when we face situations like this. He also offered to help with updating our webpages.

We also thought it would be good to shed light on the topic of child abuse and OI from different perspectives, which is why we in this magazine included an interview with a geneticist, a parent who was accused of child abuse and two radiologists.

This edition also includes two articles about how to include the voice of children with OI in treatment decisions and in research and development. The right to be heard – also known as children’s participation or voice of the child – is a key child rights principle outlined in article 12 and other articles of the United Nations Convention on the Rights of the Child (CRC). Unfortunately asking the children about their opinion is too often forgotten, even if it’s a very important human right.

I hope you enjoy the magazine and share it with colleagues and friends who might be interested!

Kind greetings
Ingunn Westerheim – OIFE president

What is the OIFE doing?
By Ingunn Westerheim, OIFE President

After a well-deserved summer holiday, we have been catching up with all the loose ends that developed during the time off. Finally, it was possible with face to face meetings again! And we have used the opportunity to be represented at two major international conferences including ICCBH in Dublin and OI2022 in Sheffield, where the whole interim Board of OIFE attended. We have also continued to plan the OIFE Investigator Meeting and Topical Meeting in Sweden in 2023, as well as activities in the OI & Pain project.

We are also very happy to announce that the process of reestablishing OIFE in Belgium has now come to an end. All our money has been moved from the German bank to our new functional bank KBC in Belgium. And OIFE as a legal entity in the Netherlands seized to exist on October 1st after OIFE (BE) took over all assets and liabilities. On October 23rd our member organizations will come together to elect a new and expanded Board of seven people. We are happy that this bureaucratic process is over and look forward to the future!
MEETINGS & WEBINARS
In addition to internal meetings, we have had external meetings with our normal collaborators incl. the XLH Alliance and with various new stakeholders moving into the field of OI. In addition, we have had meetings regarding the bigger clinical trials and we have been represented in regulatory meetings connected to some of the same trials. We have also attended the following meetings:

- OIFE interim board meetings June 21st, Aug 16th and Sep 26th
- Pain & OI project workshops, May 31st and June 14th
- UCB & Fundació Sant Joan de Deu, Jun 7th (IW)
- Steering Committee IMPACT survey, June 17th (IW and TvW)
- Amsterdam VUMC about the OI Variant database, June 20th (IW and CK)
- ECRD-conference, June 27th – 29th, IW attended parts and presented a digital poster about IMPACT
- Putnam Associates & Mereo, June 23rd and Aug 22nd (IW)
- EuRR-Bone patient organizations, June 27th (IW, Rebecca and Claudia)
- Kyowa Kirin International, July 29th (IW)
- Dr Joan Marini & Tracy Hart, August 3rd (IW)
- Sanofi, Aug 4th (IW and BVD)
- Quince Therapeutics intro meeting, August 16th and Aug 31st in Sheffield (IW)
- Ukraine Online OI-conference, Aug 17th (DL)
- European Haemophilia Consortium (EHC) Think Tank introduction, Sep 12th (IW)
- ERBF Focus Group discussion, Sep 13th (IW)
- Angitia Bio intro meeting, Sep 13th (IW)
- Sirana Pharma intro meeting, Sep 16th (IW)
- EURORDIS Open Academy Alumni about federations, Sep 19th (IW contributed as speaker)
- Webinar ICD-11 for rare diseases, Sep 27th (IW)

ICCBH-CONFERENCE IN DUBLIN
Inger-Margrethe, Ingunn and Tracy spent five educational and inspirational days in Dublin at the International Conference on Children’s Bone Health (ICCBH). Connected to the conference, we also paid a short visit to the ICCBH Rare Bone School on June 30th and we attended the entire XLH-Symposium on July 1st, to learn more about the rare bone condition XLH. The ICCBH conference itself brought many interesting talks on OI and other rare bone conditions, and was a clear indication that there is more research going on in the field than ever. We presented two posters from the IMPACT survey – one about the recruitment (OIFE) and one about adolescents with OI. We learned that there are now 25 genes coding for OI. We also learned about future therapies including medicines, stemcells and gene therapies, the
importance of exercise and weightbearing, how to measure OI bones with HR-pQCT and DXA, transition from pediatric to adult care and so much more. But the most important reason to attend the ICCBH was the brilliant networking opportunities. We met and talked to many dedicated and friendly rare bone doctors, who are interested in the OIFE and the work we do. We also got to know the organizations Tin Soldiers (based in South Africa), who’s mission is to detect patients with the rare bone condition FOP.

WEBINAR ON STRENGTHENING ERNs
On June 23rd OIFE was represented at a webinar about strengthening the European Reference Networks (ERNs), which include ERN BOND. The meeting brough a lot of different perspective on the opportunities and challenges of the ERNs and will be useful in our coming advocacy work. You can watch the recording here.

OI2022 IN SHEFFIELD – THE 14TH INTERNATIONAL CONFERENCE ON OI
From Aug 30th to Sep 3rd all the members of the OIFE interim Board were represented at the long-awaited 14th International Conference on Osteogenesis Imperfecta in Sheffield, UK. In addition to the OIFE Board members, there were also a number of other representatives from the OI-community incl. NFOI (NO), Care4BB, FOICH (Chile), ZOI (BE), VOI (NL). We kicked off the event with an informal OIFE dinner on August 29th.

The conference was a big success and provided an opportunity for all those engaged in research and clinical practice in the field to come together and share experiences and their latest data. A total of 290 delegates registered and 124 abstracts were accepted as posters with a further 31 oral communications. Feedback from the meeting has been extremely positive with many delegates citing the broad range of activities and opportunities as being really important to them. The next meeting will be held in Hong Kong in 2025, with the local organizer being Dr. Michael To. More information and reports from OI2022 will hopefully be included in the next OIFE Magazine 4-2022.

OIFE AT GEMSTONE-MEETING IN ROTTERDAM
On September 21st OIFE was invited to the Netherlands to share our thoughts on patient involvement and research priorities of people with OI and other rare bone conditions. The listeners were researchers belonging to the GEMSTONE network on musculoskeletal research.

The meeting took place at the Natural History museum in Rotterdam. Ingunn underlined that OI is much more than fractured bones and the importance of involving patient organizations early in the planning of research projects. A bonus was meeting our good colleagues and friends Inês Alves from ANDO Portugal and Oliver Gardiner, from the International XLH Alliance again.
ERN BOND NETWORK MEETING
On September 26th several people from the OI-community attended the online network meeting of ERN BOND - European Reference Network on Rare Bone Diseases: Rebecca (ePag) and Lida and Ralph from OIFE’s Medical Advisory Board.

Three times our life was divided into “Before” and “After”...
Written by Lyuba Petrova,
mother of a daughter with OI & chair of the Ukrainian OI-organization

THE DIAGNOSIS
First it was my daughter’s diagnosis of OI.

"Before" was joy of the birth of a long-awaited beautiful baby-daughter, registration to the best kindergarten in the city, early kids’ development methods, plans for a dance studio, mountain biking and ice-skating...

"After" – plans ruined, search of treatment options and clinicians, fighting with the Ukrainian Health system, and a few years of living with constant pain and tears. Because bone fractures were caused by the smallest thing or simply by walking. And then constant hospital admissions, ”plaster casts”, casts, and new fractures...

The only thing that encouraged me against despair, was meeting other parents of OI-kids and adults with OI.

THE VICTORIES OF THE OI-ORGANIZATION
“Before” implementation of OI treatment in Ukraine - constant bone fractures and tears of kids...

And “After”, when in 2019 all our dreams came true: early diagnostics, free pharmacological treatment, purchase of extremely expensive telescopic rods by the Government. All these had been achieved by our organization’s daily hard work.
THE WAR
On 24th of February 2022 again life was divided into “Before” and “After”...

Again, that awful feeling of helplessness and despair. The War has taken away the opportunity of Ukrainian children and adults with OI to receive high-quality medical care completely. Our healthcare system that had worked like a Swiss clock from the very first consultation, to the post-surgery rehabilitation of OI kids, was destroyed by the Russian army...

I remember calls and texts from parents of OI kids with the same question: "What's next?", "What will happen to the children?" Certainly no one from our community imagined returning to the horrors of life “Before”, with absence of treatment and constant pain from numerous fractures. The main hospital for the treatment of OI in Ukraine with medical professionals with experience in OI, was located in Kharkiv. And Kharkiv was the first city to fall under massive merciless attack. The Institute of Spine and Joint Pathology was evacuated, doctors fled to different parts of Ukraine or abroad, running away from the War...

HELP FROM THE OIFE & THE OI-COMMUNITY

We had to find new ways...again
First OIFE helped us. We were in 24/7 contact with OIFE representatives. Thanks to the clear coordination and help of Karina Prokopiuk, who lives in Denmark for a few years already, we solved the issue of finding clinicians in the EU to help Ukrainian OI refugee families. In addition, OIFE provided contact persons in most EU countries who coordinated communication with doctors on-site.

All Ukrainian children and adults with OI who fled Ukraine due to the War, found help in the EU. But our medical systems differ, so the terms of consultations, additional examinations, use of other bisphosphonate types and etc. delayed the treatment process for the refugees. In contrast to Ukraine, surgical treatment in the EU is provided only in critical situations, and scheduled surgeries are planned 2-6 months ahead. All these nuances were unacceptable for most of Ukrainian parents. There were some misunderstandings that the Ukrainian Association of Crystal People tried to solve if possible. Overall, anyone with a rare disease while outside of Ukraine, should expect a long process of diagnosis and treatment prescription, as it is connected to specificity of local medical systems operation.

THE PROJECT
However, the opportunity of getting medical care outside of Ukraine has not covered all needs of medical care for all Ukrainian OI people, as many of them still stay in Ukraine.

This is why our organization has joined the project of Internews-Ukraine "Guaranteed" (Ukr. “Гарантовано”) to do an effective communication campaign on timely OI diagnosis and effective treatment and medical care in Ukraine, and to increase awareness about this rare disorder, which is filled with myths and fake news.
Between May and July 2022 Alyona Romaniuk found the most interesting, recent and useful news items about diagnosis and treatment of OI. In addition, she posted stories from famous and brave people with OI on our social media. Currently, in terms of the project, Ukrainian OI people can get free consultations from leading OI experts, including Sergiy Khmzyov. Together with Mariya Kalashnikova we help to orient people in treatment and diagnosis options in Ukraine and abroad.

THE CONFERENCE
One of the most interesting events of the project was the first online conference on "timely diagnosis and treatment options of OI" held on the 17th of August, 2022, where talks were given by leading OI experts from Ukraine and EU. OIFE was represented by vice president Dace Liepina. You can watch the recording in Ukrainian language here.

So already “After” the start of the war, we try to move on and live on. Despite the war and all new challenges, so that kids and adults with OI can receive the vital treatment they need. Our battle goes on, to save the progress in the treatment of OI in Ukraine that was achieved "Before" the war.

Wrongly accused of child abuse

*Interview with Sofie Hellström, mother of Gabriel, affected by a milder form of OI type 4*

**Who are you and what is your relationship to OI?**
My name is Sofie Hellström, I am 31 years old and I was introduced to OI in the summer 2020 when my son was diagnosed with a milder form of type 4. Since no case is the other alike, I usually say he is a “type Gabriel”.

**Tell us what happened when you got accused of child abuse?**
Gabriel was diagnosed at the age of 1. Prior to that he was unfortunately misdiagnosed several times by different doctors, which led to a few untreated fractures. To fast forward to the day we were accused, it was in spring 2020, Gabriel broke his right femur while falling on grass. We sought medical attention and the doctor immediately responded that we had to go for X-ray. At that moment, with our previous experience of injuries, I asked if Gabriel could have brittle bones, whereby the doctor answered that children cannot have such a thing as bone fragility. Thereafter the investigation started with suspected child abuse. Gabriel was forced to go through CT scans, retinal examinations etc. Due to the facts that Gabriel had no signs or symptoms of head trauma, it seemed very odd to suggest such an intervention. What we later found out, was that they suspected the “Shaken Baby Syndrome”. A diagnosis that’s controversial and doesn’t have sufficient scientific support. This has been confirmed by the Swedish independent governmental organ SBU (Swedish Agency for Health Technology Assessment and Assessment of social services). It is a diagnosis that has been widely criticized around the world, but is still being used by many health care professionals. We were interrogated and investigated by social services and had to live with a safety person 24/7 for six weeks until Gabriel finally got his diagnosis. It is sad to say, but our family were lucky, in comparison to many others.

**Do you know how common this is among families with OI in Sweden? In other countries?**
It is unfortunately very common that medical conditions, where symptoms are similar to child abuse, gets misdiagnosed. Especially within those cases where there is a spontaneous mutation. At our first visit with the OI specialists, they mentioned that most of the families with children who have spontaneous mutations, go through the same process with allegations of abuse. I have also been in contact with several families in Sweden and other countries and they confirm they have been through the same, similar or worse experiences.
You have engaged yourself in a Swedish organization for families of children with medical conditions who have been accused of child abuse - can you tell us about their work?

I am engaged in an organization which helps affected families with support and knowledge about differential diagnoses. To be accused of abusing your child, is a very vulnerable situation to be in and traumatic for anyone involved. We have members who have been imprisoned, separated from their infants and thereafter released by the Supreme Court and compensated by the state due to wrongful conviction. Since the Swedish legal processes always take a very long time, the child often remains in foster care even though the parents are shown to be innocent after years of investigation. Because of time, not cause! Thus, bereaved from parents, siblings and the whole “family tree”. That is an irreparable damage that violates several human rights.

Our organization also works to make sure all children receive a good quality medical assessment. That requires that health care professionals work in a scientific way and not base their hypothesis upon the highly controversial diagnosis Shaken Baby Syndrome.

How should the OI-organizations deal with this complex topic?

Yes, the topic is very complex. However, our job is not to take sides or decide whether someone is guilty or not. It is very important that neither health care professionals nor organizations try to be the judges. Since diagnosis made by health care professionals usually become decisive in court, it is crucial that that judgement is based on science, objectiveness and correct knowledge about all differential diagnoses. It is also important that social authorities do their own objective investigation to see if there are risk factors of abuse. In our organization we have seen a lot of similarities between the cases. They are ordinary families without any reported history of violence, drugs, alcohol (risk factors of child abuse). All families have sought care on their own initiative and the children have rarely showed any symptoms of being in severe pain or had visual signs of outer trauma.

What should the organizations avoid doing?

The organizations should avoid distancing themselves from the situation. To respond by not responding should be avoided at all costs. These families are put in an extremely vulnerable situation, and the organizations should therefore work as an objective part who can support with knowledge or guide the family through the process. Having support can make a tremendous difference in the aftermath and decrease the risk for Posttraumatic Stress Syndrome.
How can we as OIFE and OI-organizations educate healthcare professionals and the wider OI-community on how to discriminate between OI and child abuse?

Again, it is not our job to “discriminate” between OI and child abuse. That is something for the legal justice system and social authorities to investigate. However, the majority of organizations know this is not an unfamiliar dilemma linked to OI or other medical conditions such as EDS, Rickets etc. Therefore, we need to make sure that more light is shed upon the conditions and especially the milder forms that is usually being misdiagnosed. We also need to learn from each case and not generalize that all children with milder forms of OI share the exact same symptoms.

Some recommendations to pass forward to health care professionals:

1. Decrease the current knowledge-gap about differential diagnoses!
2. Only use updated examination methods that has sufficient scientific proof. Stop putting children without signs of head trauma through unnecessary risky examinations linked to the controversial Shaken baby Syndrome.
3. Stay objective! Our brains are wired in the way, that if we believe it is abuse, our brains will automatically look for any confirmation to prove that hypothesis. Being biased increases the chance of misdiagnosis. This can become the crucial factor that leads to separating children from their parents and the conviction of innocent people.
4. Learn from previous mistakes! Stay humble to the fact that the situation is not always black and white, and you do not always have the answers to all questions.

We need to protect children from abuse, but it is equally important to prevent them from being separated from their families on the wrong basis. It is important to remember that attachment trauma is a harmful experience that can affect the child throughout its whole life.

What is your peer advice to parents of children with OI who might end up in a situation like yours?
Get help and support from family and friends. Make sure your child gets a thorough medical assessment and reach out to support organizations.

In Norway the OI-organization did educational talks for pediatric radiologists about OI and child abuse - would you encourage other OI-organizations to do the same?
Yes! The knowledge is too low and should be increased worldwide. Any educational talk for pediatricians is very much encouraged. I would also encourage widening the description of milder forms of OI. In the theory books, Gabriel doesn’t fit the general description of OI. It is therefore important to understand that milder forms of OI come in many variants with different symptoms.
Child abuse & OI - from the geneticist perspective

Interview with Professor Gerard Pals, biochemist (MSc) and geneticist (PhD)
at the VU university hospital in Amsterdam, The Netherlands

Who are you and what is your relationship to OI?
I am a biochemist (MSc) and geneticist (PhD). In 1989 I started a diagnostic laboratory for DNA and protein testing of inherited diseases, including OI, at the VU university hospital in Amsterdam, The Netherlands. This is now part of the Amsterdam University Medical Centers (AUMC). We do not only perform genetic testing of OI, but we are also involved in research. Our laboratory has grown from two people in 1989 to more than 200 now.

I am still affiliated with the AUMC, where I play an advisory role in OI research. I am also working 6 months per year in Indonesia, as a professor of human genetics at several universities and setting up a laboratory for genetic testing of inherited diseases at Prodia Widyahusada Tbk in Jakarta, Indonesia.

My experience with OI is in diagnostic testing and research over the past 32 years. Our team has been involved in diagnostic testing of around 1600 patients and we have discovered several new genes involved in recessive and X-linked OI. We are currently working on developing medication for OI that targets the primary problem of the collagen synthesis. We are also developing new gene therapy technology for OI.

Our center has been accredited as an expert center for inherited bone disorders by the Netherlands Federation of University hospitals (NFU) and the ERNs. As director of a genetic testing laboratory, which is a national reference center for many inherited diseases including OI, it has been my responsibility to ensure differential diagnosis in cases of suspected child abuse. If such cases were handled in court, it was also my task to act as expert witness. Because of my expertise in the field of brittle bones, I am still often asked to give advice and act as expert witness in cases of suspected non-accidental injury. Requests come from many countries.

What should the OI-organizations do when they are contacted by parents who have been accused?
The basic problem with suspected child abuse is the fact that the threshold for reporting has been made very low, without any attention for differential diagnosis. In many countries this leads to a situation where Child Protection Services (CPS) or similar organizations with different names, immediately take a child away from the parents after a referral of suspected non-accidental injury (NAI). Subsequently, the CPS doctors start looking for evidence of abuse, often without looking for alternative explanations for the reported injuries. Of course, I realize that child abuse is very serious and should be prevented wherever possible. However, the effect of removing a child from innocent, loving parents is extremely damaging to the child and to the family. In my extensive experience the CPS doctors often do not realize this. I have also noticed that, when I ask medical students or young doctors about NAI, there is no attention at all in the medical curriculum for differential diagnosis in cases of suspected NAI.

It is usually thought that OI is extremely rare and highly unlikely to be found in cases of suspected child abuse. The doctors who are involved do not realize that children with OI, whose parents do not have OI, have an almost 100% chance of unexplained fractures in their first year of life. As a consequence, they have an almost 100% chance of being taken away from their parents due to suspected child abuse. Because of this, the frequency of OI in a setting of suspected child abuse is estimated to be 1 in 15, a thousand time higher than in the general population! (See Pals and Stolk, Am J Roentgenol. 2021 Oct; 217(4):1019).
I do realize that also a child with OI can be abused. That is a very sad situation, but extremely rare. In such cases, I suggest additional evidence of abuse is required. The OIFE and other OI organizations should not get involved with individual cases. However, they should create more awareness of the problem. Individual families that approach the organizations can be referred to organizations such as ADIKIA in France or The Innocence project worldwide, or to people like myself.

What steps should be taken when an OI-family has been accused of child abuse?
The first step should be to try and prevent separation from the parents. This separation is very damaging to the child, even if there has indeed been NAI. Supervision by social services, as is the common situation in The Netherlands, is in most cases sufficient to prevent further possible abuse and prevents unnecessary damage to the child.

The next step should be to convince the CPS doctors of the necessity of differential diagnosis. It is often very difficult to break through their tunnel vision, but it is necessary. The parents are usually not believed in such cases, so they should get support from an unbiased doctor, if possible. If there is a good relationship with the family doctor, he or she may be able to help.

Genetic testing is the next step, but this in most countries very tricky, because of the ignorance regarding genetics and statistics among doctors. In my experience, the CPS often orders a test of the dominant genes (COL1A1, COL1A2) only. There is an assumption that these are the most common cause of OI and they conclude from a negative test, result that OI can be excluded. They do not realize that, if the parents do not have OI, a recessive gene is a much more likely cause of OI. Our laboratory performs a panel test of 41 genes, related to OI and other causes of brittle bones, in cases of suspected child abuse. But even this comprehensive test cannot exclude OI. Not all mutations can be detected, even with the most advanced techniques, and not all OI-causing genes are known. Moreover, I have not found a single laboratory in any of the countries in which I am active, that offers a comprehensive test for OI. Also, very recent findings show that at least ten additional genes can cause a transient form of brittle bones during the first year of life.
**What kind of genes are causing OI?**

I have concluded that 30% of OI cases are associated with non-collagen genes. This is probably a low estimate, because most of the non-collagen OI genes have only been discovered in the past ten years and have not yet been tested in all OI patients. Moreover, I have been involved in more than 1600 cases of diagnostic testing for OI and we still have not found causative gene variants in 10% of clinically proven OI cases. It is also argued that the recessive OI genes only cause very severe cases of OI, which can be easily diagnosed without genetic testing. Our recent findings have shown that this is certainly not true. We often find OI type I in families with recessive OI. This misconception is probably caused by the fact that we as researchers started looking for new OI genes in the most severely affected families.

In cases where there are children with OI from parents with no OI, the cause can either be a new mutation in one of the COL1 genes (Col1A1 or Col1A2), or due to mutations in a recessive gene. In my lab, the most common new mutation we found in COL1A1 is a deletion of the entire gene. This kind of mutation cannot be detected by most laboratories, because only the intact gene allele on the other chromosome is sequenced. For this purpose we developed the MLPA technology.

**Can you explain this further?**

Most of the variation in genes is caused by change of a single nucleotide or building block of the DNA. However, sometimes larger changes are found. This happens when during copying of the chromosomes a part of the DNA sequence is skipped. Normally we have two copies of each collagen gene, one on the chromosome that we inherit from the mother and one from the father. Sometimes the mutation is so large that one complete copy of the COL1A1 gene is missing. This is called a large deletion. The resulting lower production of collagen 1α1 protein leads to OI type I. This is the most common new mutation that we see in children with OI whose parents do not have OI. This type of mutation cannot be detected by regular DNA sequence analysis, because this only will show the sequence of the normal gene that is present on the other chromosome. To solve this problem, we have developed a technology, called Multiplex Ligation Mediated Probe amplification (MLPA) which is nowadays the gold standard in detection of large deletions and duplications (see MLPA.com). Our publication in Nucleic Acids Research (NAR 2002; 30:e57) has been cited thousands of times. With the latest DNA sequencing technology, Next Generation Sequencing (NGS), if used properly, it is possible to detect large deletions and duplications. However, most DNA testing laboratories do not perform this analysis.
What can we as OIFE or OI-organizations do to create awareness and/or improve the situation?

You can create awareness of the fact that, in a situation of suspected child abuse, OI is not rare at all! This is an important step. This can be done with publications in journals that have a broad audience among doctors and health professionals. Also websites are a good place for this kind of information.

The fact that some types and combinations of fractures are considered to be “highly specific for NAI” is extremely damaging for OI families. These types and combinations of fractures, such as “multiple fractures in different stages of healing” are actually highly specific for OI.

The extremely one-sided emphasis, in the curriculum of medical professions, on prevention of abuse is also an important issue. The OIFE could draw attention to this problem and ask for more emphasis on taking differential diagnosis much more seriously.

The situation of families in cases of suspected child abuse is actually a humanitarian and legal issue. These families lose their children without any form of process and the parents are forced to prove their innocence to stay out of prison and have a tiny chance of getting their child back. This is preposterous. What happened to “innocent until proven guilty”?

Regarding this human rights issue, a complaint has been deposited at the European Court of Human Rights on behalf of 150 French families, against the French Health Authorities and the French Government. I hope we win this case, as it will get a lot of media attention. In Florida we have gone even further, by filing federal charges against the CPS, regarding abduction, child trafficking and abuse (all with convincing evidence). This is getting national media attention in the USA.

Child abuse & OI – the perspective of a pediatric radiologist

Interview with Professor Amaka Offiah,
University of Sheffield and honorary consultant pediatric radiologist at Sheffield Children's Hospital

Who are you and what is your relationship to OI?
I work as a professor at the University of Sheffield, employed by the University of Sheffield but I am also an honorary consultant pediatric radiologist at Sheffield Children's Hospital. My interest in radiology is within the musculoskeletal system which is bones and joints, and in particular child abuse and conditions that might be mistaken for child abuse. One of the most frequent conditions that needs to be excluded and certainly considered in every case of a young child, presenting with unexplained fractures, is OI. In addition to doing research on fragile bones, I am the radiologist that leads a multidisciplinary National Commission Group (NCG), a special service for OI in Sheffield. And as such I read all the radiographs for OI. I also do the reporting for Bristol. I also get radiographs from across the country for a second opinion.
Is it hard to distinguish between OI-fractures and child abuse?
In the interest of objectivity, a child may have OI and be abused. So it’s not like the two may not co-exist. It’s just that if a child is diagnosed with OI, the benefit of the doubt must be given to the parents that they haven’t abused their child. There are also some types of fractures, that are rarely if ever seen in OI. If that fracture was seen, even if the diagnosis of OI was made, it would still be suspicious that that particular fracture had been inflicted.

In addition to findings on x-rays there are also clinical findings. Does the child have blue sclerae, loose joints and laxed ligaments? Is there a family history? On the x-rays the sorts of things we look for are slender bones, or bones with reduced density. We also look for multiple wormian bones, which are little islands of bone in the skull. Then of course there’s genetic testing, which will confirm the vast majority — like 90-95% through genetic tests. But that does not leave rest of the cases that are not yet solved. We have got an MRC funded project, which will try and help us identify more genes in children and families where they have clear clinical and radiographic features of OI, but where we still haven’t found a mutation.

A child with mild OI can look healthy and might just be a little bit shorter. They don’t have to have multiple fractures, and they don’t have to have any of those other extra features that I was talking about. So yes, it’s difficult. And in the age group where we’re talking about physical abuse, that’s usually under one (sometimes two). But under the age of one, is usually when they have their fractures. It can therefore be hard to distinguish. Not every child with OI has blue sclerae. And at that age, the teeth are not yet erupted. So we cannot look for DI either.

There is a type of fracture, at the very very end of the long bones, called metaphysial fractures. These are rarely if ever caused by OI or just by normal handling of the child. We’ve done a project and we didn’t identify any cases with a metaphysial fracture in an OI-case. We have reviewed a large number of radiographs of children with confirmed OI under the age of two. So I think the presence of that type of fracture is an indication of abuse, even if the child has OI.

What are the methods of distinguishing brittle from normal bones?
The current techniques for distinguishing brittle from normal bones is essentially radiographs. But they’re not sensitive. You have to have lost up to 30% of your bone, before you can see that on the radiographs.

So if the child has lost 10 or 15% of their bone density, then it’s hard to see that from the radiographs. There are papers which say that, until you have lost about 30%, then you’re not prone to fractures. I don’t know that true that is.

The other current technique would be Dual-energy X-ray absorptiometry, also known as DEXA (or DXA). Used a lot for women and adults, predominantly women with osteoporosis. And DEXA is not particularly reliable in children of the age, where abuse is suspected. It has to do with having normal values, to do with their body size and to do with the fact that DEXA is size related.

In older adults they do something called peripheral quantitative computed tomography pQCT. And then there is QCT which is quantitative CT, that usually looks at the spine. We wouldn’t use any of these techniques to assess bone density in children, because they are high dose.
Then, there are some promising new methods. In particular, there's high resolution PCT (HRpQCT), which has been a fair bit of research on lately. It gives you microscopic level on details of children's bones. It's not a high radiation dose. But there are only a few machines in the world. So it's very much connected to research.

But what we're trying to do also is to compare that with something called bone health index, which you can measure from X-rays of the hands. If we can set values for bone health index that correlate with abnormal values for HRpQCT, then that would be a really good thing. Because we could give people the conversion values. If it's above the cut off level, the child is likely to have normal bone density and bone strength. And vice versa.

We've also tried to develop vibration, as a method of assessing bone density. Many of these studies have unfortunately been delayed and stalled by the lockdown.

What are the best imaging methods to diagnose fractures in OI?
The best imaging method for diagnosing fractures, has got to be the standard X-ray. It's widely available. It's relatively low cost and you don't need any specialist individuals to help you identify the fractures. However, it's not perfect. Nothing is.

We’re trying to investigate more about the metaphyseal fractures, which we see in child abuse. Can ultrasound maybe be useful to help identify the metaphyseal fractures after X-ray shows potential abnormality?

CT of the chest, might also be useful for subtle rib fractures. But usually in the context of OI, the fractures are not subtle. The fractures are multiple, and we would be able to detect those on X-rays.

Why do fractures sometimes don’t show until a couple of days after the incident?
Unless the fracture is displaced, you may not see it. If the edges of the broken bone are not shifted away from each other, so they're not aligned correctly, you may not necessarily see the fracture. It becomes visible a few days later because of healing. Fracture healing can be seen on radiographs as early as day four. Usually, sometimes by day seven. Most commonly, by day 10, and always by day 14, you’d see radiographic evidence of healing.

And sometimes just taking more X-rays from a different angle, allows us to see the change or the malalignment of the fracture, which wasn’t possible to see before.
How should OI-organizations deal with potential child abuse cases?
In the context of child abuse, the doctors are only interested in the child. The child is our priority. Is the organization there for the child or for the parents, or for both? They have to be supported, but with objectivity all the way through. Even for the health professionals, nobody knows who the guilty party is. And until investigations have been completed thoroughly, nobody knows whether it's abuse or OI. Or both.

What are the steps that are taken when a family has been accused of child abuse and there is a potential OI-diagnosis?
I will answer this from my own perspective, as a pediatric radiologist. I receive the request card and I receive the radiographs. If I only have a single radiograph, I will ask for full sets of radiographs of the whole body to be performed. When you're suspecting abuse, you have to image every single bone in the body, because you don't know which bone has been broken by the perpetrator.

If some x-rays are poor quality, I will ask for these to be repeated. When I’m satisfied to have all the images needed, I will review them all very carefully, identify all the fractures, that I see. I will give an estimate of dates of the older fractures that I see, and I will also look at the bones, to try and identify or exclude an underlying condition.

If that was the first set of radiographs, I will say within my report, that they must be repeated according to Royal College of Radiology 2017 guidelines in about 11 to 14 days’ time. And until I see these repeated radiographs in 11 to 14 days time, I cannot completely exclude abuse. However, if on that set of initial radiographs, I identify features which are definitely those of OI, or other underlying conditions, I will say that.

“When we can see features of OI, we don't go ahead and say it is abuse, except in the situation where we may see those metaphysical fractures. If we see the metaphysical fractures, we might say this looks like a combination of OI and abuse.”

I’m then relaying my findings to my pediatric colleagues. Especially if the X-rays were completely normal. Because ultimately the diagnosis of OI is not based on the X-rays. It is based on clinical and genetic findings. They will go back and review the child. But that again, you know, considering that the X-rays are normal. And decide on clinical parameters, whether they need to do genetic tests or not. Sometimes if they don’t, the court will ask for genetic tests, just for closure.

The other thing is that the social services, and the pediatricians will identify whether there are other siblings in the house, or other family members or other children who are not related living in the house that that child lives in who are under two. And all of those children, will also have to be investigated and imaged according to the guidelines.

Do you have a message to the readers of the OIFE Magazine?
There is hope! There are people out there, people like myself, doing research, trying to make the diagnosis of OI more straightforward. We’re trying our best not to mistake OI for abuse, while at the same time, not leaving abused children in dangerous environments.

Amaka gave a lecture about diagnosing fractures in OI in Sheffield.
HR-pQCT: A revolution in bone imaging

Interview with Bettina Willie,
Professor at McGill University and Shriners Hospital for Children in Montreal, Canada

Who are you and what is your relationship to OI?
I am Bettina Willie, and grew up in Utah, US. I earned a doctoral degree in Bioengineering from the University of Utah and I did my first postdoctoral training at the Institute of Orthopaedic Research and Biomechanics at the University of Ulm in Germany. I then did a second postdoc at the Hospital for Special Surgery, in New York City. I maintained my connection to Germany by working as a group leader in the Julius Wolff Institute at the Charité – Universitätsmedizin Berlin for nearly eight years. My research was then focused on examining how mechanical loading influenced bone formation and healing during skeletal aging and in rare bone disorders. Since 2015, I have worked as a Professor at McGill University and Shriners Hospital for Children in Montreal, Canada. There I decided to start a research program on OI myself. I use multidisciplinary approaches, including high-resolution imaging to find out how to treat bones that break easily.

Some of my research involves scanning people with OI using high-resolution imaging, called high resolution peripheral quantitative computed tomography (HR-pQCT). I served as the central reader for a recently completed Phase 2b, multinational, double-blind, dose-finding study in adults with Type I, III or IV OI treated with a new drug called Setrusumab. As the central reader, I was in charge of determining how we scan the participants, analyzing all the HR-pQCT data, and helping the 13 clinical scanning sites in the UK, France, Denmark, Canada and the US when they had questions. As part of this study, we also determined how reproducible the HR-pQCT scanning was in people with OI, which was published in the medical journal Bone (Mikolajewicz et al. 2021). My laboratory also developed different methods of scanning people with OI over time to find the same volume of bone and we tested how reproducible these methods were (Tabatabaei et al JBMRI 2022). I make all of my lab’s methods and software codes publicly available at a website called Github, so that other scientists can freely use them.

Together with Dr. Frank Rauch and Dr. Francis Glorieux at the Shriners, I am currently performing the first study that uses HR-pQCT to scan children with OI over time to see how their bone structure changes. I have learned a lot from this study in terms of various challenges scanning and analyzing data from kids with OI as well as children in general. Since the bones of children are growing, it is challenging to image the same volume of bone at the beginning of the experiment and at one year follow up. My lab will determine if image analysis methods (called imaged registration methods) that are commonly used in adults can also be implemented in children. In addition, although there are standard imaging protocols established for adults, there is no consensus on where one should scan the bone of children. This has led to difficulty in comparing HR-pQCT data from different studies. There is a pressing need to standardize HR-pQCT scanning and data analysis methods in children.
I am also interested in learning why bones from people with OI break so easily. Our skeletons adapt to increased mechanical loading by forming more bone. For example, tennis players have denser bone in their playing arm than their nonplaying arm. A lack of mechanical loading can also lead to reduced bone mass. When a person does not get enough physical activity, the skeleton adapts by removing bone tissue. This often occurs with astronauts, individuals with paralysis or people who are bedridden for long periods of time. What’s more, bones have a reduced ability to adapt to mechanical loading as people age. Research shows exercises that promote bone formation in young people aren’t as effective in middle-aged or elderly people. But the molecular mechanisms involved in this altered response with aging are unclear. There is some evidence that the bones of people with OI may also have an altered response to mechanical loading. Dr. Frank Rauch and I recently received a five-year grant from the Canadian Institutes of Health Research to examine the bone formation response to mechanical loading in mice with OI.

**What do you do when you are not working?**

I am married with two sons. Both of my children have health issues, which has motivated me even more to focus my research on a disease that affects children in particular. I relax by spending time with my family, working in my garden, reading mystery novels, or watching the Toronto Blue Jays baseball team.

**What it HR-pQCT?**

HR-pQCT is a powerful imaging method that gives information on the bone’s structure and mineral density in the arms and legs. This allows us to estimate the bone’s strength and ability to resist fracture.

**What is the difference between imaging methods when it comes to measuring bone density/quality in OI?**

An X-ray is like a shadow of the bone that provides some qualitative information, including if the bone is fractured. DXA allows some quantitative information about the bone’s density. A normal CT scan allows for a 3-dimensional image of the bone, but bone density cannot be measured. To measure bone density, quantitative CT (QCT) must be performed. HR-pQCT is a form of QCT, which is limited to the peripheral bones (ie. arms and legs), but has a higher image resolution compared to QCT, enabling the assessment of the bone’s structure.

**What are the best imaging methods to diagnose fractures in OI?**

Fractures are usually easy to diagnose on X-rays. In some cases, it is necessary to use CT, MRI or DXA.

**What kind of imaging has the lower/higher radiation doses?**

HR-pQCT is a low radiation dose method; the effective radiation dose from a standard scan at the distal radius or tibia is 3–5 μSv. This is lower compared to other common medical imaging techniques. For example, a hip scan using dual-energy X-ray absorptiometry (DXA) has an effective dose of approximately 9 μSv, a standard chest X-ray approximately 100 μSv, and a hip CT scan 2000–3000 μSv. The amount of natural radiation that children would have during a day at home in North America is an effective dose of 8 μSv.

**Why are there so few HR-pQCT machines worldwide?**

HR-pQCT were introduced relatively recently; the first-generation scanners were introduced in 2004 and the second-generation scanners in 2014. Also, they are a relatively costly device priced at approximately $500,000 US.
What are the opportunities and challenges of HR-pQCT in OI?
Some challenges are that not many studies have been done in healthy children, so we do not know exactly how different the results are in children with OI. Also, it can be more difficult to position the individual’s arm or leg within the device, especially for people with more severe OI types, who have shorter or deformed limbs. The opportunity of HR-pQCT is to calculate bone strength better than with other techniques.

How can this be solved with standardization?
The expert teams that work on a similar HR-pQCT topic can collaborate to share their methodologies and data. This enables an evidence-based comparison of different methods performing a similar task, which could facilitate us reaching an agreement. These collaborations can result in consensus publications that provide recommendation for the community, which will also increase the impact of the work that each group has done.

Are HR-pQCT parameters predictive of fractures?
Currently, DXA is the most common imaging method used to assess bone mineral density and predict fracture risk. However, it is far from perfect, and many people still have bone fractures despite scoring high on their DXA bone scan. HR-pQCT allows us to measure the bone density more accurately than with DXA and it allows us to measure the bone’s structure and strength. Together with other experts in the field, I performed a review of all the studies that had been conducted using HR-pQCT (called a meta-analysis).

We found that HR-pQCT measures of bone density, structure, and strength were significantly lower in people with a prior fracture (Mikolajewicz et al. JBMR 2020). Another group calling themselves the Bone Microarchitecture International Consortium (BoMIC), also looked at a large number of previous studies using HR-pQCT and they found that bone density, structure and strength measured using HR-pQCT were important predictors of fracture and they were able to predict fractures better than only using bone mineral density measured by DXA (Samelson et al. Lancet 2018).

In what kind of research projects have HR-pQCT been used as an outcome measure?
The HR-pQCT scanner was first designed for osteoporosis research in adults. However, the use of HR-pQCT has not been limited to osteoporosis. An increasing number of studies are being performed to examine a certain disorder or a particular drug treatment over time.

You encourage professionals who work with OI & HR-pQCT to collaborate more?
I highly encourage the experts working with HR-pQCT to collaborate to facilitate the standardization of HR-pQCT scanning techniques in children and how they report methods. I am open to collaborating with other experts on these topics as well as share any of our methods.

See more information and contact details under the Get in touch column!
Project: participation of children with OI in health care

Interview with Jenny Wang, Shriners Hospitals for Children (SHC) – Canada and Khadidja Chougui, PhD candidate in clinical child and adolescent psychology at Université de Montréal, Canada

Jenny Wang: My name is Yi Wen (Jenny) Wang, and I graduated from McGill University with a Bachelor of Science Nursing degree in 2019 and a Master of Education degree in 2021. My work in OI started when I was awarded the McGill University Faculty of Medicine Research Bursary in 2018, which led me to start working at the Shriners Hospitals for Children (SHC) – Canada under the supervision of Dr. Argerie Tsimicalis and Dr. Franco Carnevale on the project Moral Experiences of Children with Osteogenesis Imperfecta. I now continue to collaborate with the team at SHC-Canada to contribute to the development of tools and resources that address the needs of children with OI and their families.

Khadidja Chougui: My name is Khadidja Chougui, and I am a PhD candidate in clinical child and adolescent psychology at Université de Montréal. I have a long-standing relationship with the SHC-Canada as myself, have OI type III. I joined the nursing research team, led by Dr. Argerie Tsimicalis, in 2015, when I had just graduated from McGill University with a Bachelor of Arts and was looking to gain more research experience. I have worked on many OI-related research projects, including the Moral Experiences of Children with Osteogenesis Imperfecta.

*Please note that most responses were written by both Khadidja and Jenny. Certain questions (specified) were answered by Khadidja only.

What was your research project about?
Phases 1 and 2 involved using art-making to elicit children’s voices and explore their desired and actual participation in health-related discussions, decisions and actions in the OI hospital and community. We collected data from interviews with 10 children with OI, observations and field notes, children’s art (e.g., drawings, paintings, fictional stories, and dolls), and 57 local documents to help us learn about the study context. Building on previous phases, Phase 3 involved convening stakeholders to disseminate findings, identify ethical concerns and generate action steps, resources and tools that enhance clinicians’ abilities to engage with children, and navigate ethical concerns in children’s OI care. The product of Phase 3 was an ethical framework and clinician worksheet to optimise the participation of children with OI in their healthcare.

What were your most interesting findings?
We found that children often experienced anger, frustration, and disappointment when they felt excluded from their care. In contrast, alternative forms of communication such as art-making facilitated their self-expression and helped them to participate more actively in their care.

Any surprising findings?
The notion that children should participate in their care is becoming increasingly accepted. Despite children’s desires, active involvement in their care is sometimes missing due to a lack of child-oriented educational resources and/or encouragement from adults around them. Art-making appeared to attenuate some of these challenges as it helped children to reveal things about their experiences that they otherwise wouldn’t have disclosed.
Are there any differences between children with OI and children with other conditions?

Khadidja: The voices of children with medical conditions are not always heard or given due weight when making important decisions about their care. This can be further exacerbated in children with OI due to their characteristically short stature, making them look younger than they are. Often healthcare professionals talk primarily to parents rather than the patient, which can contribute to the experience of anger, frustration, and disappointment reported in our study. That is why we must find ways to facilitate communication as children do not always express themselves in the same way that adults or adolescents do.

What is the most important take-home message for clinical work?
Children’s voices are not limited to speech, and it is crucial for healthcare providers to provide opportunities for children to express themselves. Since a lack of hospital resources can hinder clinicians’ abilities to engage children in their care, our studies fill critical gaps in children’s OI care by showcasing the value of alternative forms of communication and the necessity for resources and tools (such as the ethical framework we developed) which may help healthcare providers engage with children.

Did you have any form of patient involvement in the planning/implementation of the project?
I (Khadidja) have been a member of the research team since 2015. Dr. Tsimicalis has always believed in patient engagement, even before it had become the latest buzzword. She was looking for an academic with OI to bring their unique perspective gained through the lived experience of this condition. In this specific project, I was involved from the beginning to the end. It always warms my heart when participants light up, when they see themselves in me, and it has helped facilitate recruitment and study participation. My input during data analysis has always been valued and respected, which has led to many enriching discussions that allowed us to learn from one another.

Any messages for the readers of OIFE Magazine?
Thank you for the opportunity to showcase our work! We hope that our research project helps to highlight the value of child-centric research methods, particularly in children with rare conditions and chronic illnesses, as well as the untapped potential for further research opportunities using these methods to develop tools and resources to improve their care.
International Children’s Advisory Network (iCAN) Summit 2022 in Lyon

By Dace Liepina, OIFE Vice President

The iCAN Summit 2022 took place in Lyon, France. It was an event for young people aged 12 to 19 from all around the world to meet, exchange ideas and learn more about rare diseases and children’s rights, health and data protection. Many of the young participants were living with a chronic or rare disease, but some did not have any diagnosed medical condition. All were interested in having their voices heard by individuals, industry and government agencies who can make a difference in pediatric healthcare.

In July my daughter Emilija, thanks to a grant from European Joint Programme on Rare Diseases (EJP RD), provided by TEDDY - European Network of Excellence for Paediatric Research, had an opportunity to participate in iCAN Summit 2022, which took place in Lyon, France. It is an event for young people aged 12 to 19 from all around the world to meet, exchange ideas and learn more about rare diseases and children’s rights, health, and data protection.

In 5 days packed with information, kids aged 12-19 were participating in different workshops, listening to presentations, and learning how to be Young Patient Advocates.

Day one was an introduction to rare diseases with sessions like learning about rare diseases and its environment, connecting patients in rare diseases, children rights, health and data protection and a presentation by EURORDIS on young citizens participation in European policies.

Day two started with a presentation about ethics and rare diseases, followed by information about pediatric research and innovation and about assessment and appraisal of new drugs. In the evening was activity in city center – play and discover Lyon.

Next morning, we met at Lyon Hospital to have a tour around the hospital. Afterwards there were presentations about transition and therapeutic education, adapted physical activity and mobile apps and GDPR. Then all kids were divided into 4 groups and had case simulations and some physical activities.

The fourth day was filled with group work all day long. In the evening we went out to city to have a party to celebrate Bastille day. It was so great to see all the young people dancing, playing games, singing, taking pictures and talking, talking, talking. Also, we as parents had a possibility to network and enjoy the beautiful summer evening which ended with fireworks.

The last day of the summit was dedicated to group work and presentations. Both me and Emilija loved the possibility to learn a lot of new things and most of all to meet with new people from all over the world.
**Update on our Pain & OI Project**

*By Ingunn Westerheim, OIFE President*

**Background**

Pain is reported to be the main challenge for people with OI besides fractures. More than 60 percent of people with OI have chronic pain, and the percentage and complexity increase with age. In spite of this, there is very little information about how you can manage pain as a child or adult with OI. There is also little knowledge and awareness about different kinds of pain in OI among people with OI and professionals.

**An international resource group**

On January 25th 2022 we organized the kick-off of the Pain & OI project, which is a collaboration between the OIFE and the OIF (USA). It includes a group of dedicated professionals who have experience on pain management, pain research and/or pain & OI. Originally it was thought to be more of a fixed expert group, but people change jobs, projects and priorities. So we have renamed it to an international resource group on pain & OI. We have also included some experts on other rare bone conditions than OI.

At the moment, the resource group includes 27 participants from 11 different countries, covering both pediatric and adult professionals. It’s a very multidisciplinary group which include PTs, orthopaedic surgeons, endocrinologists, rheumatologists, anaesthesiologists, pain specialists, psychologists, paediatricians, researchers, nurses and a social worker. The group also include three people who have OI themselves. In addition, we are three representatives from OIFE, who contribute with the perspectives of adults with OI and parents of children with OI.

We have agreed on these common goals:

1. Recommendations on how to assess pain in OI incl. different kinds of pain
2. Recommendations on how to measure pain in OI (over time) in the clinic and in clinical trials
3. Educational activities about OI & pain to various target groups
4. A toolbox on management of chronic pain for children and adults with OI

We have had three constructive workshops in 2022 so far and we’re planning the fourth one. Our goal is to present some results at the Topical Meeting “Balancing life with OI” in Stockholm from June 8-11th 2023, where pain will be one of the main topics.

In addition, OIFE and the OIF are involved in another industry sponsored project related to OI & pain, which includes literature search and qualitative interviews.

Some important questions to discuss:

- How does pain in OI differ from pain in other conditions?
- What is the connection between OI pain & hypermobility, sleep, fatigue, soft tissue, inflammation, obesity, and arthritis?
- How can we prevent chronic pain by providing better acute pain management?
- Do pain diaries make sense? Are people motivated to use them?
- Will ICD-11 provide a better classification system for chronic pain?
- What is the connection between pain and physical function in OI?
• Which coping strategies are most beneficial when it comes to pain & OI? Do people with OI ignore (cope with) their pain for too long?
• Are there factors that help buffer mental health problems because of pain? Ex: peer support, parental support, coping, resilience etc?

In the upcoming editions of the OIFE Magazine we will include at least one (but probably several) articles on pain and OI produced by the members of the resource group. The first one out is Mercedes Rodriguez Celin, who works in Chicago.

A review on pain, OI and bisphosphonates

Interview with Mercedes Rodriguez Celin, pediatrician at Shriners Hospital for Children, Chicago

Who are you & what experience do you have with Pain & OI?
I am Mercedes Rodriguez Celin; I am a pediatrician from Argentina with a specialty in Growth and Development. I worked for ten years at the Skeletal Dysplasia Clinic at Garrahan Pediatric Hospital, Buenos Aires. Since I moved to the US 5 years ago, I have been doing clinical research in OI at Shriners Hospital for Children, Chicago and most recently completing a Postdoctoral Fellowship in Advanced Rehabilitation Research Training through NIDILRR. I had the opportunity of treating many patients with OI over the years, and I have been involved in many research studies that directly or indirectly analyzed pain in OI.

Tell us about the project “Do Bisphosphonates alleviate pain in children? A systematic review”.
We were invited by Current Osteoporosis Reports to review this topic, as our OI research group at Shriners Hospital for Children Chicago has previously been working on related topics such as mobility, rodding, and the effectiveness of bisphosphonates (BPs) to improve mobility in OI. Also, at that point, we were starting to develop our proposal to conduct the "Multicenter Study of Pain Characteristics in OI", so this question was aligned with our research topics and interests.

We decided to conduct a systematic review, so that we could use rigorous and transparent methods to summarize all the available evidence in the literature. We included all the publications from the last ten years (2010-2019) where the pain was measured in children and adolescents under BPs treatment. We included studies done on OI and on a wide range of skeletal diseases to understand better the role of BPs in alleviating bone pain.

How was it financed?
My work has been financed through Shriners Hospital for Children, the Orthopaedic and Rehabilitation Engineering Center (OREC) at Marquette University in Milwaukee, WI and a grant from the U.S. Department of Health and Human Services.

How do you define pain?
Pain has been defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Interestingly in the last few years, the definition was expanded to include relevant concepts such as: always considering pain as a personal experience that might be influenced by multiple factors. The IASP also reinforces the importance of respecting an individual's pain report. Additionally, the IASP recognized that pain might have adverse effects on function and social and psychological well-being.
So, if I have to define pain, I would say that pain is a personal and complex experience with components of the individual’s physical, emotional and psychosocial aspects. Therefore, we are speaking about a multidimensional experience that needs to be addressed and understood.

**Are there different types of pain that people with OI struggle with?**
Pain has been broadly categorized as acute or chronic, depending on the duration, but some patients may have an overlap between these types of pain. The IASP has adopted three major divisions to classify pain as nociceptive, neuropathic, or nociplastic, depending on actual or threatened tissue damage, or the lesion of the somatosensory system causing the pain, or pain that arises from altered nociception (nervous system processing), respectively. Also, pain could be classified regarding the source of pain as bone pain, joint pain, muscle pain, etc. Some individuals with OI may have pain from different sources and in various sites at the same time. Therefore, pain in OI could be complex and multifactorial.

**What were your most interesting findings from the review?**
We found that more than 80% of the studies included in the systematic review reported a positive effect of BPs for alleviating pain in different pathologies, but 58% of the studies were categorized as having a high risk of bias. So, we concluded that intravenous BPs might help alleviate bone pain in children and adolescents. However, we advised that our results should be interpreted with caution due to the heterogeneity of doses used, the duration of treatments, and the types of conditions included. Our review shows the lack of high-quality evidence in the available literature. Future research should prospectively study the effectiveness of BPs using a control group or placebo when possible. I was surprised by the wide variety of pediatric conditions, other than OI, that uses BPs for pain relief. For example, we found that BPs were used for pain relief for conditions such as osteonecrosis related to chemotherapy, chronic non-bacterial osteitis, and unresectable benign bone tumor.

**What is the most important take-home message for clinical work?**
It is essential to keep in mind that BPs are widely used in adults to treat osteoporosis, and they have been used for their analgesic effect in several bone-related conditions. However, in children, BPs are used off-label for many conditions to improve bone density and decrease fracture risk. So, if the decision to use BPs for pain relief is made, providers and families should consider that the scientific evidence for this recommendation in children is weak. Therefore, we encourage to monitor clinically the real benefits of using this medication to treat bone pain.

**In one of your talks, you called pain in OI “The elephant in the room”. What did you mean?**
We decided to refer to pain as “the elephant in the room” because, in many opportunities, we might want to avoid addressing and managing “the pain issue.”
As we explained before, the pain might be complex, multifactorial, and challenging to treat in OI, so providers, patients, and families could have difficulties approaching this topic. Therefore a multidisciplinary approach to pain would be essential to dealing with pain in OI.

**What is the most important topic the pain & OI resource group should focus on?**
It has been described that pain is not only an unpleasant but also disabling experience in OI. Therefore, this group has many challenges ahead regarding improving the assessment and treatment of pain in OI. But, in my opinion, we should start by trying to improve the evaluation of pain. So, in that aspect, we should work as a team, exploring which are the available validated, multidimensional tools to assess pain that could be more useful in individuals with OI. A better understanding of pain may help delineate the possible causes and identify the more optimal treatments for each patient.

**Artists with OI: Kristian Keogh**

Kristian is an Australian professional video editor and graphic designer. He is using a wheelchair, but this didn’t stop him from making a dream come true: performing with the Bangalow Theatre Company doing the Musical "RENT", his favorite musical. Kristian also talks for instance about daily challenges and the situation of people with a disability in Australia.

**Can you tell us a bit about yourself?**
Hi my name is Kristian Keogh. I live in Lismore, New South Wales, Australia. I have a Bachelor’s in Media, specifically screen media. I am a professional video editor and graphic designer. My hobbies include and are not limited to playing power wheelchair tennis, swimming, music (Jazz Singer, Piano), content creation, streaming on YouTube and Twitch, video games and more.

**How does OI and the need of your wheelchair affect your daily life?**
OI affects your life on the regular, broken or not. Thankfully I have the most incredible supports that have helped me during the tough times and times when a wheelchair cannot access things that I want to be involved in. Nothing is truly off limits, and I think any OI person’s main strength is to find another way to do the things you want to do.

**You are living with a cat. What are the challenges? For instance, I can imagine that especially a cat's tail is extremely threatened by the wheels of your wheelchair...**
My cat Mercy is almost 5 years old now, and I am planning on getting another little kitten very, very soon. The main challenges in the beginning were of course with Mercy when she came home with me as a tiny 7-week-old kitten in 2017. Like, “how was I going to feed her from the floor?” So, I got a small table to be a raised feeding spot for her, among other solutions. It’s funny you mention the tail because nowadays she trusts me so much, she likes to do trust exercises with me where her tail is millimeters away from my tires. She’s so used to wheelchairs, she gets trodden on by able bodied people all the time, almost daily!

**Can you describe a little where and how you live?**
I live in an accessible unit/house in a complex of other houses. Everything in the house was modified to help me live as independent as possible. My house is two bedrooms. My second bedroom is a studio for my video recording and music stuff and is incredibly nerdy. Town is a quick 5-minute drive away. Sadly, there is no safe non-car way for me to travel into the town itself, but the CBD is reasonably fine to just go around in a power chair. At the current moment I do not have my own vehicle as it is getting modified. But once I get it, I will be able to do a lot of things on my own.
How is the situation of people with a disability in Australia?

This is a tricky one! Where I live is rural town, accessible public transport is only attainable and 100% safe via wheelchair accessible maxi taxis, of which there are about 5 of them for the entire town area. But in major capital cities like Sydney, accessible public transport includes, trains, light rail (trams), buses and taxis and they are in abundance with plenty of new stations and stops being made accessible. Access to medicine is pretty good in public system but with OI, it can be a challenge to get the right surgeon and care so I always recommend getting private health insurance to help with you getting the best you can for yourself, and you miss the long waitlists of the public system. Of course, only do that if you can afford to do so. Most Aussie doctors in the public system will do their best to put you onto the right people regardless, but that can mean travelling fair distances as not all hospitals are equipped for OI and just for regular patient issues.

Australia is a huge country. What difference does it make for people with a disability if you are living in a city or in the outback? Are you well connected?

In major cities help is far more plentiful, but they are expensive to live in. Lots of places in the city as far as I have seen, are also not the most wheelchair friendly either or that accessible. As you move further from cities, help can be a bit harder to gain and requires more research. However, thanks to the National Disability Insurance Scheme (NDIS), help is never too far away or hard to find. Basically, the more remote you are, there will be different challenges and hassles. The NDIS allows people with disabilities to live as independently as they can. It’s a body of funding that pays support workers, assistive equipment like wheelchairs etc. Participants on the scheme, like myself, can then access their community and do a lot more things than before the scheme. As a 26-year-old person, it can sometimes be a cramp in style and a dilemma to bring your Mum or Dad out of their work or own plans to have them attend something you are interested in and they’re not. So, having the NDIS pay support workers who are keen to support you and the things you want to do is a major plus.

In a video you give the following statement: "To most people with any disability it’s hard to find a work that will adapt to you." Can you explain what you mean by this?

Finding the right place to work can be extremely tricky. It really depends on what you want to do for work and how willing the company and/or employers are willing to adapt their workspace to accommodate you. I think during and post COVID, this adaptation expands to the work from home. Technology and the internet make finding a home job even easier to the point where I hope other people with disabilities look at what they can do in their home. You’re no longer bound by country or location! It’s awesome!

You recently performed with the Bangalow Theatre Company doing the Musical "RENT"?

RENT is absolutely my favorite musical of all time. Followed closely by Matilda and Lion King. RENT tells the story of a group of young, impoverished artists living in lower New York City at the turn of the millennium and the AIDS epidemic. It isn’t your typical musical as it is very much rock orientated and very 90s. It deals with HIV/AIDS, LGBT and many more issues that nowadays are more commonplace and widely accepted. Back in the 90s the ideas of gay marriage were still a fiction. It started with my mum tagging me in a comment of a post the Bangalow Theatre Company (BTC) posted on their Facebook page that was advertising auditions for RENT in 2019. I was initially a bit hesitant to audition because I was unsure of the wheelchair access of venue. After talking to the BTC organisers they showed me photos of the venue. It was accessible, including the stage! So, I immediately went for audition. I found out a few weeks later I was in the ensemble cast. And I was ecstatic to do something I thought I’d never do in my life, perform in my favorite musical.
Were there any challenges regarding this project?
We started rehearsing in January 2020 but then COVID hit so all of us in the company were not sure if we could perform. Some of us pulled out but I decided to wait for 2021 to see if it would go ahead. Rehearsals restarted early 2021 and we had a 2-week season performing the show in June. The scale of the entire production was immense. The directors and the set designers worked closely with me to ensure the set was workable for a wheelchair and even the choreography of dance was chair adapted which BTC had never done before.

What was the most positive experience during this project?
Honestly, how willing and supporting everyone was not just of me being a cast member with a disability, but it was the first time since 2013 that I had acted in theatre, and I was welcomed as a part of the BTC and RENT family. All the cast and crew were. I am truly thankful and honored they welcomed me in to be a part of their production and I cannot wait to do more with them again. Check out this video for a small glimpse.

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Open access genetic testing program

The Discover Dysplasias® program provides individuals suspected of having an inherited skeletal dysplasia (incl. OI) access to high-quality genetic testing. Early access to testing can enable an accurate diagnosis, which can lead to improved patient outcomes.

Blueprint Genetics and BioMarin collaborate to offer a no-cost 419-gene panel for the diagnosis of the genetic cause of skeletal dysplasias (incl. OI). This program is available for individuals in certain countries in Europe and the Middle East who meet the eligibility criteria. The comprehensive testing strategy in this program offers increased potential for establishing a molecular diagnosis. For more Information on eligibility, participation and the complete list of countries follow this link.
Get in Touch!

ANTONELLA SEARCHING DOCTORAL CANDIDATE
Professor Antonella Forlino (member of OIFE MAB) is searching a doctoral candidate for her team who will deeply phenotype a murine model of OI to investigate the aging effect of misfolded collagen type I on multi-organ failure. CHANGE is a Marie Sklodowska-Curie Doctoral Network (MSCA-DN) focused on investigating connective tissue (CT) disorders to identify key players in age-related decline in physiological functions to develop therapeutic strategies and identify treatment targets for common diseases and frailty associated with aging. It is part of Horizon EUROPE programme of the European Union and 12 Doctoral Candidates (DC) will be appointed for 36 months each. Read more here: https://euraxess.ec.europa.eu/jobs/812870

BETTINA WILLIE SEARCHING PROFESSIONALS USING HRpQCT!
Did you read the interview with Bettina Williw about HRpQCT? Do you work with HRpQCT in children and is interested in standardizing HR-pQCT scanning methods in kids? Bettina would like to organize an online meeting with stakeholders to come to a consensus on HR-pQCT scanning parameters for children, so that data can be better compared between studies. The goal would then be to write a consensus article outlining these scanning parameters. Her email address is bwillie@shriners.mcgill.ca

LIDA ZHYTNIK IS SEARCHING FOR COLLEAGUES IN AMSTERDAM
Our MAB-member Lida Zhytnik is looking for colleagues who would be interested in the opportunity to join Amsterdam UMC OI team. The research group has one open PhD student position. Available for applicants with MSc degree in cell biology, molecular biology, gene- or biotechnology or equivalent. Also, Amsterdam UMC OI team would like to find a researcher with PhD degree or current PhD candidate from Ukraine, who is interested to write a MSCA4Ukraine grant together. The group is working on the development of a therapy for Osteogenesis Imperfecta.

If interested, email l.zhytnik@amsterdamumc.nl

Research Announcement Update

The TOPaZ trial receives funding for a 24 month extension
The TOPAZ trial has received funding for an additional 24 months to compensate for the interruption of recruitment imposed by the COVID-19 pandemic. The trial is designed to determine if anabolic therapy with Teriparatide (TPTD) followed by a single infusion of zoledronic acid (ZA) is superior to standard care in adults with osteogenesis imperfecta (OI). The trial is open to anyone over 18 years with OI whether or not they have previously been treated. The only exception is people who have received anabolic therapies in the past two years.
The trial now has 25 study centres actively recruiting in the UK with additional European centres in Dublin, Paris and Amsterdam. A new study centre is being added in Zwolle, the Netherlands, where the local PI is Dr Hans Feenstra, and in Aarhus, Denmark where the local PI is Professor Bente Langdahl.

Professor Stuart H Ralston the Chief investigator said “We are delighted that the funder has granted this 24 month extension which will allow us to complete this important study which has been designed to determine if TPTD and ZA is more effective than standard care at preventing fractures in adults with OI.”

At the present time the investigators have recruited 310 people which makes it the largest every clinical trial in adults with osteogenesis imperfecta by a long way (Figure).

The investigators are aiming to reach their target of 350 before recruitment is scheduled to close at the end of November 2022. With the additional funding the study is due to run until the end of 2024, with closeout scheduled for April 2025.

If you are interested in taking part in the study please feel free to email the study team on topaz.trial@ed.ac.uk or Professor Stuart H Ralston, the Chief Investigator on stuart.ralston@ed.ac.uk for further information.

News in brief

MEET DR. TO – THE HOST OF OI2025
We have had the pleasure to meet Dr. Michael To, from Hong Kong, at several international conferences. This included OIFE’s topical meeting in 2015. Dr. To is one of the most experienced OI-surgeons in the world. He has operated more than 1000 people with OI and is working closely with the two OI-organizations in China. He’s also going to be the host of the next scientific OI-conference in Hong Kong in 2025. Recently a documentary about him was shown in Hong Kong television. You can see it (in Chinese language) here: https://bit.ly/3E0BidB

CALLING OI-RESEARCHERS!
Check out the OIF’s Michael Geisman Fellowship Grant awards funding to post-doctoral trainees who are currently working on projects with clear relevance to OI, or who have projects that will enable them to develop expertise in OI research. Apply today at www.oif.org/geismanapp

NEWS FROM NATURAL HISTORY STUDY
Check out the latest updates on osteogenesis imperfecta research from the Brittle Bone Disorders Consortium (BBDC) and the OIF with Dr. Reid Sutton of Baylor College of Medicine! http://youtu.be/qG5RBlv4T1M
NEW POTENTIAL RNA TREATMENT FOR OI
The German biotech company Sirana Pharma has entered into a collaborative research agreement with Pfizer Inc. to investigate the potential identification and validation of a novel treatment concept for OI. The collaboration will utilize Sirana’s microRNA (miRNA)-targeting approach, which targets substantial regenerative recovery of diseased muscle and bone tissue. Source: https://bit.ly/3SAQK4B

NEWS FROM OI-RESEARCH
There are more and more potential treatments for OI being investigated. Through this large European repurposing project, the blood pressure drug Losartan will be tested as a potential drug to improve bone density in OI. Stay tuned for more information: https://remedi4all.org/

PATIENT EXPERT TRAINING
Are you interested in becoming a patient expert? You can now register for the European Patients' Academy on Therapeutic Innovation (EUPATI) Patient Expert Training Programme! Join a growing network of EUPATI fellows and patient experts, and gain a thorough understanding of research, development and patient involvement. Register before 1 November 2022: https://bit.ly/BecomeEUPATIFellow

IRDIRC REGULATORY COMMITTE
The International Rare Diseases Research Consortium (IRDIRC) announces creation of regulatory scientific committee to tackle regulatory challenges in rare diseases. Read more here: https://bit.ly/3RhnA9f
the resources (processes, tools and systems, organisational structure) needed within the OI-organisation. Enrol now: [https://cutt.ly/gZEriSR](https://cutt.ly/gZEriSR)

**(RE)HABILITATION FOR ALL AGE GROUPS**

Did you think that rehab is only to regain function after fractures? Rehabilitation can also be an important factor in getting more fit or in improving daily life functions. Jon-Kristian and Rebecca from Norway attended rehab courses at Beitostølen Helsesport-senter (BHSS), where people with disabilities or diseases can come and try out new activities and exercise. Read more about what BHSS offer: [https://www.bhss.no/om-senteret/beitostoelen-healthsports-center](https://www.bhss.no/om-senteret/beitostoelen-healthsports-center)

**QUALITY OF LIFE OF ADULTS WITH OI**

A new review article summarizes 17 studies of quality of life of adults with osteogenesis imperfecta (OI) over the last 20 years. Dr. Kara Ayers made some infographics, to illustrate the findings in an easier way. Read the whole review article here: [https://bit.ly/3Cha3dw](https://bit.ly/3Cha3dw)

**COURSE ABOUT COMPETING INTERESTS**

More and more commercial stakeholders are moving into the field of OI. This is good news, but can also bring some complexity. The European Calcified Tissue Society (ECTS) has developed a course on how competing interests can be managed in a multi-stakeholder environment to make engagement in medicines development easier for all. Enrol now: [http://l.eurordis.org/YyXu](http://l.eurordis.org/YyXu)

**OI & NUTRITION**

Check out the new Factsheet from the OI Foundation (USA) called «Nutrition and OI»! The factsheet highlights various factors important to overall health and serves as a great introduction on how nutrition can contribute to improved bone health. Check it out at [www.oif.org/factsheets](http://www.oif.org/factsheets)!

**NEW BOOK ABOUT OI IN SPANISH**

The project Share4Rare in Barcelona, Spain has created a web-based book with medical resources on OI. The plan is to translate it to English later. [https://bit.ly/3E3FZ6h](https://bit.ly/3E3FZ6h)
NEW SOLO ALBUM - MICHEL PETRUCCIANI
The famous jazz pianist with OI Michel Petrucciani died in 1999. But still new recordings from the musical genius are being released. The latest record called "Solo in Denmark" was released on September 2nd 2022. Read more here: https://bit.ly/3SuE3IE

TALKING ABOUT LIFE EXPECTANCY
Check out this really good blogpost by Samantha Renke from the UK, which covers the topic of life expectancy in OI and how difficult this can be to talk about. Read it here: https://bit.ly/3rhKAKM

GREETINGS FROM CANADA!
How much fun was is to be at summer camp organized by the Canadian Osteogenesis Imperfecta Society, who recently applied for associate membership with the OIFE.

FIRST PHD ON PAIN & OI
We congratulate the Spanish psychologist Ruben Munoz with the publication of his PhD thesis “Chronic pain in adults with osteogenesis imperfecta and its relationship with personality, appraisal, coping and quality of life: a descriptive study.”. The PhD can be downloaded here in Spanish language: https://bit.ly/3fO9YF8 OIFE has access to an unofficial English language version.

GREETINGS FROM TAIWAN
The Taiwanese OI organization has recently had focus on teeth and dental health. Experienced dentists came to meetings to do examinations and provide advice.
Topical Meeting
Stockholm June 8-11-2023
"Balancing life with OI"

Subtopics will include:
- pain
- fatigue
- sleep
- mobility
- family and relationships.

Collaboration with Swedish OI group (SPOI)

Venue: Scandic Continental
Walking distance from airport express
25 wheelchair accessible rooms

Target group:
- People with OI & parents of children with OI
- Clinicians and researchers
- Anyone else interested in OI

OIFE TOPOICAL MEETING
OIFE topical meeting is open for anyone interested – including people with OI, OI-parents, researchers, clinicians, industry and others with an interest in OI. The main topic will be pain & OI, but as you can see, we are also including other topics connected to “Balancing life with OI”. We will open registration soon.

REGISTRATION FOR OIFE INVESTIGATOR MEETING IS OPEN
OIFE is together with members from our MAB inviting you to register for the very first virtual European Investigator Meeting for OI. Register here:

OIFE Calendar
For an updated list of events & conferences - see OIFE’s web calendar: http://bit.ly/36A6mw8

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