OSTEOGENESIS IMPERFECTA
FEDERATION EUROPE

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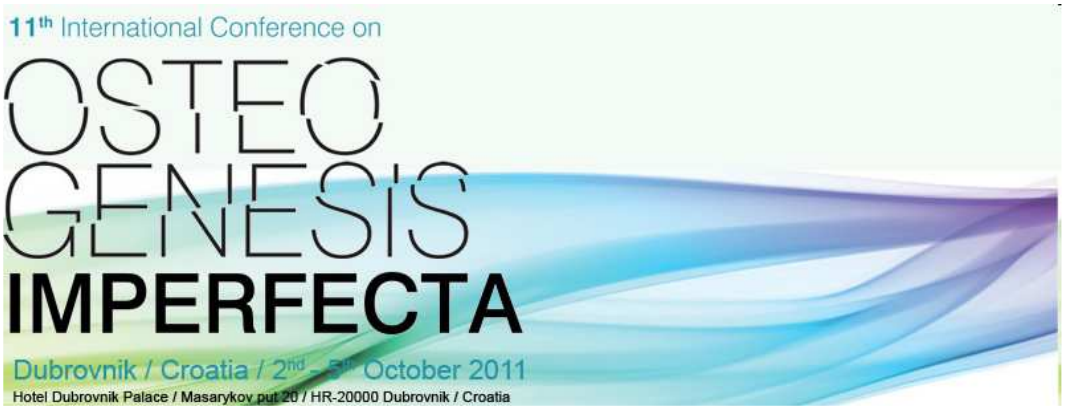
Special Edition

New developments reported from the 11th International Conference on OI – Dubrovnik 2-5 October 2011



Projects:

The International Conference on OI is organized by different hosts every three years, in 2011 it took place in Dubrovnik/Croatia from 2nd – 5th October 2011. Its Scientific Committee consists of the president and 17 members, all medical and scientific experts on OI. They had received more than 110 abstracts in advance and chose 57 different presentations for the 2,5-days-program. The topics were mixed from a wide range of scientific and clinical medical topics that had attracted participants from all fields of expertise.

Some 150 people from at least 30 countries from 5 continents attended this meeting, among them 13 representatives of the OIFE and various national OI associations. Also at least 20 OI-surgeons where present to exchange knowledge and experience. The historic city of Dubrovnik on the Adriatic coast provided a breathtaking scenery for the conference, though most of the time was spent indoors in the modern hotel to follow the full but very well organised program. OIFE was invited to give 2 presentations. Ute Wallentin spoke at the start of the meeting explaining about the goals and activities of the OIFE, Taco van Welzenis later gave a presentation about the situation of OI adults. Pictures and the list of participants will become available here:
http://www.conventa.hr/osteogenesis.imperfecta2011/index.html

Remember:

Latin-American OI-Congress in Quito, Ecuador: Dec. 5th-11th 2011

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Student Exchange program:

Would you like **to host** an OI-student? Please contact OIFE if you can help. Thank you!

Recessive forms of OI

Our understanding of OI as a disease caused by dominant mutations in either one of the genes COL1A1 or COL1A2 needs adjustment. In the past few years recessive mutations in at least 7 other genes have been linked to mostly severe and lethal types of OI. And even more genes await discovery as not all cases of OI can be linked to the genes known today. The recessive forms of OI are all quite rare, together they represent less than 10% of cases in the West-European Caucasian population, however the frequency of recessive mutations varies a lot between populations meaning that ethnic background has implications for genetic counseling in OI.

Darko Antičević, member of the Scientific Committee and host of the Scientific Conference

Classification

The original Sillence classification of OI in 4 clinical types had already been expanded with the recognition of types V and VI. (Type V with ossification of a membrane between the bones of the forearm and hyperplastic callus formation, and type VI with a mineralization defect). A trend in the literature has emerged to add a new OI type for each newly identified gene. E.g. types VII, VIII and IX have been proposed for OI caused by mutations in genes CRTAP, LEPRE1 and PPIB respectively. These 3 genes code for the 3 parts of a complex that is necessary for the correct synthesis of collagen. In addition OI due to mutations in SERPINH1 was labeled type X while the gene SERPINF1 has been linked to the previously described OI type VI. Yet another gene, FKBP10 has been linked to OI type XI and it was shown that it shows overlap with previously described disease called "Bruck syndrome type I" which is now presumed to be a manifestation of the same disease. A mutation in the gene SP7 causes a disease that looks very much like OI as well.

The question is what consequence this should have for classification? When these new "genetic" types are added to the existing "clinical"

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Sillence types the problem is that different criteria are used which are not mutually exclusive. For example a person could have OI type III based on clinical grounds, but when you study his DNA it could be one of the new recessive types. Geneticists argue of course that in that case "real" OI type I-IV should be reserved for the cases caused by mutations in the collagen genes. However that means that without genetic testing it would be impossible to classify OI properly in many cases. Not unimportant since testing is expensive and not available to the majority of the world population.

There is still some debate going on about the question how much specific clinical symptoms accompany the various recessive forms, but some scientists say the clinical differences do not justify the new types and argue in favor of abandoning the genetic types, and to only uphold clinical types I-V (or VI), and then to add the gene in case it happens to be known. A similar recommendation was given by a nosology (disease classifying) committee, it recommended to abandon the numerical classification of OI and proposed 5 purely clinically defined OI types, based on the Sillence types, with the addition of a fifth type; OI with calcification in inter-osseous membranes (type V), the other types would then be; non-deforming OI with blue sclera (type I); perinatally lethal OI (type II); progressively deforming OI (type III) and common variable OI (type IV).

On the other hand it is clear that when studying disease mechanisms, drug therapies or providing genetic counseling it is crucial to distinguish between the different genes. The flipside is also that a clinical classification separates patients with a very similar biochemical problem that happen to have a different clinical outcome, for instance lethal or non-lethal, as having different OI types. Further problems with the clinical classification are that because of advances in therapy especially the kids with more severe types of OI have improved so much that it becomes harder to distinguish them based on deformities and fractures alone, also the clinical type can sometimes not be clear at birth or even later in life. Obviously a need for both a clinical and genetic approach is evident and the last word has not been spoken.

New therapeutic approaches

With the increase in our understanding of the (many) pathways that can give rise to OI, more ideas about potential drug therapies evolve as well. We start to get some insight in the question why some people don't respond to bisphosphonate therapy. For instance people with OI type VI having a different disease pathway in which there is a problem with the protein PEDF, at the same time this pathway opens possibilities for a different therapy especially for this group of patients. Mouse models for almost all forms of OI exist now and these have been instrumental in gaining knowledge. Compiling the results of mutation studies in a huge database (more than 1500 different OI mutations have been reported) shows that sometimes the exact same mutation can have a different outcome, for instance type II or type III. This means that other factors such as treatment or other genes influence the outcome. We now start to get glimpses of factors that cause this variation. One genetic factor

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which was shown to be of importance was the SOST gene, it makes a product, sclerostin, which helps to break down bone. The thing is, like with blood groups, that different versions of this gene exist in the population. Some people will have a version that works a little harder at breaking down bone, others are more "lazy". It was shown that people with OI who have two hard working copies of the SOST gene have more fractures than those with one copy or two lazy copies. Further studies show that mice with OI that were given antibodies to sclerostin get stronger bones so this is an interesting thing to research further. Substances which inhibit the formation of osteoclasts (bone eating cells) like RANK-Fc and Denosumab are being tested in OI mice as well, a similar result as from bisphosphonate treatment was reported, it is important to note that so far the results are only valid for mice, in humans further studies about side effects and dosage are still necessary. Gene therapy is another thing which is studied in OI mice – one idea is for instance to take cells from which the bone forming cells grow, then to silence the OI gene and then to put these cells back in the body. In theory this could change a more severe type of OI into a milder form.

Part of the audience

OI in adults and secondary features

Following a presentation of OIFE's vice-president Taco van Welzenis about OI adults several presentations referred to adult OI patients and there was general consensus that new and better structures for OI-adults need to be developed. An article about OI adults will follow in the next edition.

Clearly OI affects more than just the bones. Dental problems, hearing loss, spinal deformities and respiratory function as well as cardiovascular function have to be addressed. Hearing loss occurs in about half of the patients, it is hypothesized to be connected to low trabecular bone mineral density. An increase in the prevalence of mild and moderate regurgitation of mitral and aortic valves was reported but no instances of

OIFE's objectives:

*Representing its members on a European level
*Presenting the problems and needs of people with OI to national and international organizations
*Collecting and publishing information about OI
*Promoting research on all aspects of OI
*Supporting member-societies by the exchange of information and experiences
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severe regurgitation were seen. Mild mitral regurgitation was also common in the control group. In lung function tests it was recommended to measure arm span diameter (not height) in OI. Parents and children are often afraid to have spinal fusion surgery performed, however in the hands of an experienced orthopedic surgeon good results were reported. Some studies about psychological effects of OI looked at different perception of problems by members of the family or measured the quality of life of children and adolescents with OI. It was reported that children with OI agree with their parents that fractures need to be avoided but that an area of conflict may arise between children who strive towards independency and overcoming isolation and overprotective parents.

Treatment

There was consent about the importance of a multidisciplinary approach, consisting of e.g. pharmacological treatment with bisphosphonates, surgical correction of deformities when necessary and good rehabilitation to promote activity and prevent osteoporosis as a result of inactivity.

Bisphosphonates still seem to be the best choice for treatment of OI children and adults with low bone density, many fractures and/or bone pain. In recent years some cases of osteonecrosis of the jaw have been reported in combination with bisphosphonate use. A study of 102 children with OI treated with neridronate did not find any cases. It seemed early bisphosphonate treatment could lower the incidence of scoliosis in children with OI type III. Most common and recommended bisphosphonates remain pamidronate, zoledronic acid and neridronate (in Italy and Germany). The latest studies have shown that some oral drugs (alendronate and risedronate) are effective in OI children but results didn't differ much from placebo, so current indication is not formal (yet).

However it may be considered for older children with milder forms of OI or after initial use of intravenous treatment, but more research is still necessary. When to stop bisphosphonates is still an unanswered question, but experts recommend that bone-density levels must be monitored and treatment must be continued until the child stops growing (adjusting dose and interval). Vitamin D levels need to be regularly checked in every OI patient and substituted if found too low. As in the non-OI-population more than 50% of people have deficiency or insufficiency – but importance for calcium intake is bigger in OI patients.

Rodding of long bones: several presentations showed the advantages of Fassier Duval-rods compared to other kinds of telescopic rods; still most important seems to be the amount of experience a surgeon has with OI-bone and which kind of rods or pins etc. he/she prefers. The importance of good function of the arms was stressed – surgery in the upper extremities, especially in the forearms have not been routine in OI because of possible complications. However, the need to keep its good function has been seen by doctors of primordial importance as it may affect also the overall mobility of the person (powering a wheelchair, using crutches). When necessary, early surgical intervention by

experienced orthopedics can be recommended. The over 20 surgeons present agreed that they would have a common website set up to exchange and discuss difficult cases of surgery and experience in joint replacement surgery etc. in OI patients – for more information please contact Francois Fassier, Shriners Hospital, Montreal

Ute Wallentin, OIFE President
and Taco van Welzenis, OIFE Vice-President