Research Connections
News and Events in Shriners Hospitals for Children’s Research Department
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Osteogenesis Imperfecta: Research on Causation and Treatment

Osteogenesis imperfecta, also called brittle bone disease, is a heritable condition that leads to fragile bones. Children with osteogenesis imperfecta can have dozens of fractures while they are growing up, and often develop bowing of the legs and a curvature of the spine. The SHC-Canada is a major center for the orthopedic and medical treatment of this disorder.

Finding New Genes: Genetic tests for brittle bone disease have been available for many years, but in some patients all the routine tests are negative. This makes it difficult to inform parents who have a child with osteogenesis imperfecta whether they have a risk of having another child with the same disorder. Testing whether other family members are carriers of the disease can also only be offered if the genetic change is known in at least one family member. There are different forms of brittle bone disease. New treatments for brittle bone disease that are under development are specifically targeting the protein that is abnormal in the various forms of osteogenesis imperfecta. For all these reasons, it is important to find out the exact cause of the disease in every patient.

X-Ray of the spine (side view) of a 2-year old boy with osteogenesis imperfecta. The arrows indicate fractured vertebral bodies.

Dr. Frank Rauch at SHC-Canada, in collaboration with researchers from McGill University, has initiated research to find out the genetic cause of brittle bone disease in families, where the genes that are usually involved in this disease are normal. With the rapid advances in genetic technology, which enable a more rigorous examination of genes, it is now possible to examine all genes in the human body in a single test run. This research program has already helped to find the cause of brittle bone disease in a number of families, making surprising discoveries on the way. For example, it was found that several children treated at SHC-Canada have a change in a gene called WNT1. These children have very fragile bones and many fractures in the spine, similar to what is seen in elderly people who have osteoporosis. Before this research project made the link between WNT1 and bone fractures, this
gene was thought to be important for brain development. However, these children have normal mental development. Knowing the exact cause of the disease in these children will make it easier to develop a more effective treatment.

**Developing New Medical Treatments:** Once the cause of a heritable disease is known, it becomes possible to develop a “humanized” mouse model of the disease, which means that the abnormal gene is incorporated into a mouse. The genetic change that was discovered in patients with brittle bones can then be created in mice. In many cases the mice will then have abnormalities in their bones that resemble the condition in humans. Dr. Pierre Moffatt at SHC-Canada is developing such mouse models of *osteogenesis imperfecta*. This is done by introducing a genetic change that was previously found in a patient into the mouse gene. The offspring of this mouse can then be examined and new drug treatments can be tested in these mice. In some cases, it is possible to develop entirely new types of treatments. In any case, testing a new treatment in a mouse is an essential step before it can be used in humans.

**Helping with surgical decisions:** Children with *osteogenesis imperfecta* are often born with bowed leg bones. Once bones are bowed, even the most effective drug treatment is not sufficient to straighten them out. Rather, orthopedic surgery is needed for this purpose. About a decade ago, Dr. François Fassier, orthopedic surgeon at SHC-Canada, had developed a nail that can be inserted into the tibia of children with *osteogenesis imperfecta*. This nail keeps the tibia straight after surgery and elongates as the child grows. This method is now used worldwide to treat children with *osteogenesis imperfecta*.

In children who have milder forms of *osteogenesis imperfecta*, the bones in the legs are often bowed, but the bowing is not severe enough to prevent them from walking. In such patients it can be difficult to decide whether the risk of breaking the bone during everyday activity is so high that surgery is necessary or whether children can walk — and jump — on their legs without having a fracture. To help with this decision, researchers from SHC-Canada have teamed up with engineers from the engineering school *Ecole Polytechnique de Montreal* to develop computer models of bowed tibias. With such a computer model, it is feasible to simulate the stresses that occur inside of the bone in circumstances that may happen during a child’s everyday life, such as jumping. When these stresses are close to the point where the bone is expected to break, it will be time to perform the surgery and correct the bowing.

This image is a computer model of the bowed tibia of an 8-year old girl with *osteogenesis imperfecta*. The colors indicate the stresses that occur in the bone.

**Summary:** Children with *osteogenesis imperfecta* face many challenges that need to be addressed on many fronts. Solutions are needed for the short term, such as improved surgical decision tools, and for the long term, such as new medications that make the bones stronger and prevent fractures from happening in the first place.