Citation: IBMS BoneKEy **11**, Article number: 521 (2014) | doi:10.1038/bonekey.2014.16

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NEWS

Childhood fractures in the clinic: when is it idiopathic juvenile osteoporosis?

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IBMS BoneKEy **11,** Article number: 521 (2014) | doi:10.1038/bonekey.2014.16; published online 19 March 2014

Recent *IBMS BoneKEy/ICCBH* webinar focused on diagnostic and therapeutic approaches

When should physicians make a diagnosis of idiopathic juvenile osteoporosis (IJO), and how should they treat this rare but important and often overlooked cause of childhood fractures? Those questions were at the heart of a recent webinar cosponsored by *IBMS BoneKEy* and the *International Conference on Children's Bone Health* (*ICCBH*). The webinar featured presentations by a panel of three internationally recognized experts on pediatric bone health and disease, including Craig Langman, MD (Feinberg School of Medicine, Northwestern University and Lurie Childrens Hospital of Chicago, USA); Catherine Gordon, MD (Hasbro Children's Hospital, and Alpert Medical School of Brown University, Providence, Rhode Island, USA); and Nick Bishop (University of Sheffield, and Sheffield Children's Hospital, Sheffield, UK). The webinar program featured a number of clinical scenarios that illustrated the complexities of making a diagnosis of IJO, and also discussed the components of an appropriate treatment plan for children with the condition.

The webinar is available for viewing at: http://www.nature.com/bonekey/webinars/index.html?key=webinar31.

To put IJO into its proper context, it is first necessary to understand the epidemiology of childhood fractures, a topic to which Dr Langman turned in the first part of the webinar. He explained that fractures are quite common in children, particularly during early adolescence, and that the incidence of childhood fractures has increased over the past two decades, particularly in periadolescent girls.[1,2] Most childhood fractures occur in the periphery, particularly in the forearm, fingers and toes. 'Importantly, children do not fracture routinely in their long bones or spine,' said Dr Langman.

For children who do present with long bone or spine fractures, physicians should begin to consider osteoporosis as a possible cause. Here, Dr Langman pointed to recently proposed 2014 guidelines from the International Society for Clinical Densitometry that define osteoporosis in childhood. According to the guidelines, 'The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis, in the absence of local disease or high-energy trauma.' Furthermore, the guidelines state that 'In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and bone mineral density (BMD) Z-score $\leqslant -2.0$.' Importantly, Dr Langman said, the proposed guidelines say that 'The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone,' and the webinar panel stressed that physicians will need to broaden their focus beyond BMD per se in order to make a proper diagnosis of childhood osteoporosis.

Dr Langman then explained that there are many possible causes of osteoporosis in childhood, including monogenic causes such as osteogenesis imperfecta.[3] In addition, many chronic diseases of childhood are associated with osteoporosis, including inflammatory conditions such as juvenile idiopathic arthritis, inflammatory bowel disease and asthma. Conditions of disuse, such as cerebral palsy and spinal cord injury, can also be a cause of osteoporosis, as can the use of medications such as corticosteroids or immunosuppressive drugs. With all these possible causes, how can physicians make the differential diagnosis of IJO?

It was to that question that Dr Gordon then turned. She emphasized that the diagnosis of IJO is a diagnosis of exclusion, where the physician must first rule out systemic diseases, endocrinologic processes, or the use of medications that can be associated with bone loss. She also stressed that the clinical presentation of IJO varies, as patients can exhibit back pain, kyphosis, multiple fractures, osteopenia or difficulty walking. She also explained that IJO is often seen in school-age children (aged 7 and above), and resolves as children progress through puberty. Furthermore, the hallmark findings of IJO include low bone formation markers such as osteocalcin and alkaline phosphatase, low insulin-like growth factor-1 and low BMD assessed by dual-energy X-ray absorptiometry (DXA).

Dr Gordon also stressed that physicians evaluating children with potential IJO should consider whether there is a family history of osteoporosis or frequent fracture, as bone mass is largely controlled by genetic factors. The child's dietary history is also important for the physician to consider, particularly with regard to caloric intake, as well as intake of protein, calcium and vitamin D; physicians should be sure to rule out vitamin D deficiency, a common finding particularly during the winter in

cloudy and cold climates. Things to be aware of upon physical examination include kyphosis, loss of height, a breastbone that is sunken into the chest (pectus excavatum) and a limp, with severe cases often presenting in wheelchairs. Fortunately, children with IJO usually get better. 'Most children with IJO experience a near-to-complete recovery of their bone tissue, and typically have normal resumption of their growth thereafter,' said Dr Gordon.

The next portion of the webinar consisted of a number of clinical scenarios—one presented by Dr Gordon, and three presented by Dr Bishop—that illustrated the range of presentations of possible IJO. Dr Gordon's case, an 11-year-old girl with multiple fractures and lax joints, was initially misdiagnosed as IJO, but as a result of genetic work was later correctly diagnosed with Ehlers Danlos syndrome, revealing the importance of doing a thorough genetic analysis. Dr Bishop's three case studies revealed further key points. The first case study was that of a 14-year-old boy with a 1-year history of back pain but an otherwise unremarkable history, with normal bone biomarkers, vitamin D and blood counts, as well as a negative celiac screen. Bone density values were also in the normal range. However, plain X-rays of the spine revealed several vertebral crush fractures, likely the cause of the patient's pain. 'Having crush fractured vertebrae does mean you have osteoporosis, but it is also important to recognize IJO is a diagnosis of exclusion,' Dr Bishop emphasized. In this particular case, underlying conditions that physicians must first rule out include osteogenesis imperfecta, inflammatory disease and malignancy.

Dr Bishop's second clinical scenario was that of a 13-year-old girl with Crohn's disease who used steroids when her disease flared. The girl had no history of fractures, but her growth in height and weight were faltering. Spinal X-ray films showed normal vertebrae but very low BMD values. Here, a key teaching point was that the low BMD values observed in this patient could be consistent with the patient's small body size. Consequently, physicians need to think carefully about how to make adjustments for BMD *Z*-scores in such cases, although precisely how best to do so remains uncertain, as there are many different methods to adjust DXA-derived data for size-related artifacts; work is ongoing to illuminate this issue. A second key teaching point was that steroids are known to increase fracture risk, and so steroid-induced osteoporosis is one of the conditions that must be excluded before making a diagnosis of IJO. Finally, a third clinical scenario was that of a 9-year-old girl with back pain and limb fractures. Here the patient had osteomalacia, revealing the importance of considering that condition as a cause of a child's bone pain, fractures and low bone mass.

The webinar next turned to the question of how best to treat IJO. Here, Dr Langman addressed the issue of whether IJO improves as part of the natural history of the disease. He pointed to a small recent study of nine IJO patients, with an average age of just under 10 years, who were randomized to treatment with the bisphosphonate pamidronate or to no treatment, over the course of 7 years, with two additional years of follow-up.[4] The study found that although fracture rates were similar between the two groups at baseline, after 2 years untreated patients fractured more frequently compared with treated patients and continued to fracture more frequently over succeeding years, suggesting that bisphosphonate treatment can be warranted in IJO patients. Fracture rates in untreated patients did go down over time, suggesting that IJO does improve to some degree as part of the natural history of the condition, but the essential point was that fractures still occur as part of the natural history of IJO whether patients are treated or untreated. Furthermore, after 7 years, lumbar areal and volumetric BMD *Z*-scores were lower in untreated patients compared with those in treated patients. Overall, the limited evidence that exists suggests that patients with IJO can benefit from bisphosphonates, even if the natural course of the disease tends to improve over time. Beyond bisphosphonates, Dr Langman pointed to physical therapy, physical activity, adequate nutrition and adequate levels of vitamin D as important adjunctive therapies for IJO.

After the main presentations, the panel considered a number of intriguing questions from the listening audience. One question is how physicians should handle patients with very low bone density, but without a history of fracture. 'I always say that it is really important to treat the patient, and not the DXA scan,' said Dr Gordon. The panel agreed that in the absence of fractures or abnormal vertebrae, bisphosphonate therapy is not warranted; lifestyle and nutritional approaches are preferable here, although Dr Gordon also mentioned that bisphosphonates can be effective to relieve pain. Dr Langman and Dr Gordon said that, in their practices, a typical course of therapy with bisphosphonates is 3 years, and they do not recommend treatment beyond that time frame. In their collective experience, the panel has not observed atypical fractures in bisphosphonate-treated IJO patients, which further supports only a time-limited use of those medications.

Because IJO is thought to be a failure of osteoblasts, another question with regard to treatment is whether an anabolic drug such as teriparatide could have a therapeutic role in IJO. In this regard, one concern Dr Bishop raised is that teriparatide has been linked to osteosarcomas in preclinical studies. He said that 'An anabolic agent in the growing skeleton is something that I think we need to consider very carefully, including the potential risk of inducing malignant change, and what the potential cost versus benefit would be.' In terms of potential anabolic therapy, one exciting future possibility Dr Langman pointed to is anti-sclerostin antibody treatment, which is now being studied in experimental models of osteogenesis imperfecta.

Concerning treatment, another important question is whether clinicians should limit athletic activity in patients with IJO. 'This is the million-dollar question,' said Dr Gordon. Her practice is to limit athletic activity, particularly for teenagers who play high impact sports such as gymnastics, but she stressed that it is important not to immobilize patients; Dr Bishop agreed, noting that doing so could potentially further reduce bone mass. For IJO patients who have fractures, a return to physical activity should be cautious and gradual once a cast is removed, the panel agreed.

The final question the panel debated on was whether all children with osteoporosis should see a pediatric bone specialist. The panel concurred that it is imperative for children with osteoporosis to see doctors who have experience in treating that condition. Dr Bishop noted that such physicians tend to be based in specialist centers, where patients also have access to multidisciplinary teams with valuable expertise in a number of different areas, such as physiotherapy and occupational therapy. Dr Gordon added that who the pediatric bone

specialist is can vary from community to community and could be a pediatric orthopedist, nephrologist or endocrinologist, or perhaps a general pediatrician with expertise in treating IJO, so it will be important to identify a physician in the community who has the proper clinical expertise and experience for treating the IJO patient.

Conflict of Interest

The author declares no conflict of interest.

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