



# Osteogenesis imperfecta

## Principal investigator

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## Background

### The clinical spectrum of osteogenesis imperfecta

Four different types of osteogenesis imperfecta (OI) are commonly distinguished on the basis of clinical features and disease severity, according to the classification proposed by Silience.<sup>1</sup> Patients with OI type I have a mild phenotype with normal or near-normal height and typically blue sclerae, while OI type II is usually lethal in the perinatal period. OI type III, known as progressive deforming OI, is the most severe form in children surviving the neonatal period. These patients have a characteristic phenotype, including extreme short stature, severe deformity of the spine, thoracic cage and extremities, white or blue sclerae and often a triangular facies. Patients with a moderate to severe form of the disease who do not fit one of the above descriptions are classified with OI type IV; as such, this group is extremely heterogeneous. Patients with OI type I represent 60% of OI, followed by OI type III (20%), type II (10%) and type IV (< 10%).

In the majority of cases, OI is inherited as an autosomal dominant trait, though autosomal recessive transmission and gonadal mosaicism have also been described. In about 85% of OI patients, mutations in the genes encoding type I collagen, COL1A1 and COL1A2, can be found. Thus, although collagen type I



mutations are frequent in OI, the lack of a detectable mutation does not rule out the diagnosis.

Recently, the Sillence classification for OI has been expanded, by characterizing three groups of OI patients (named OI types V, VI and VII) with distinct clinical and histological features. Patients with OI type V demonstrate a striking radiological triad of hypertrophic callus formation, interosseous calcification of the forearm, and a dense metaphyseal band under the growth plate.<sup>2</sup> The inheritance suggests autosomal dominant transmission. On iliac crest bone biopsy specimens, there is a loss of the normal pattern of lamellar bone in OI type V, often with “mesh-like” appearance.

Patients with the OI type VI phenotype show subtle distinguishing clinical features, such as normal sclerae and teeth. There is a moderate elevation in alkaline phosphatase levels, as well as characteristic histological features that include increased osteoid thickness and disordered bone lamellation.<sup>3</sup> Despite these histological signs of a mineralization defect, there is no evidence for a disorder of mineral metabolism, and mineralization of the growth plate is unaffected. The mode of inheritance in OI type VI is unknown.

OI type VII follows autosomal recessive inheritance, and was recently described in a consanguineous First Nations community from Northern Quebec.<sup>4</sup> Rhizomelia and coxa vara are striking characteristics of the disease, associated with slightly blue sclerae, normal dentition, and moderately severe long bone deformity. This form of OI has been linked to chromosome 3p, outside the type I collagen loci.<sup>5</sup> The precise genetic defect of OI type VII remains to be elucidated.

### **The changing face of OI: bisphosphonate therapy**

In recent years, the quality of life for children with severe OI has improved remarkably through the administration of cyclical intravenous pamidronate, in conjunction with multi-disciplinary (surgical and rehabilitative) care.<sup>6,7</sup> Pamidronate is a bisphosphonate drug that is thought to exert its beneficial effect through inhibition of bone resorption. After the start of pamidronate therapy, bone pain disappears, mobility improves and fracture rates decrease. It appears that the best response to pamidronate therapy occurs in children who are first treated in infancy.<sup>7</sup> These findings highlight the importance of prompt diagnosis and initiation of medical and supportive therapy during early life. In addition to intravenous pamidronate, studies of other bisphosphonates, including oral agents, are ongoing, with the aim to provide clinicians with a variety of treatment options for patients with OI of differing severities.



## ***Osteogenesis imperfecta (continued)***

### **Incidence of OI and the need for current incidence data**

The most reliable estimates of the frequency of OI to date are based upon reports of fractures occurring in the newborn period. However, neonatal fractures are unlikely in OI type I, and may or may not occur in OI types III to VII. While the incidence of the disease is estimated to be 1:20,000 to 1:60,000 live births, the true incidence of OI is likely to be much higher. These estimates were established more than 15 years ago, before newer diagnostic techniques (collagen mutation analysis, bone densitometry) became widely available.

There are no prior reports of OI incidence in Canada. A recent review of OI patients treated at the Shriners Hospital of Montreal revealed that of 220 Canadian paediatric OI patients, 58% were from the province of Quebec, 25% were from Ontario, and 30% were from the remaining provinces and territories. These results suggest that patients more distant from this paediatric OI program may remain undiagnosed and go without specific OI treatment or may be treated in other centres. Since a Canadian registry for OI patients does not exist and many patients with OI will not be hospitalized (thus eliminating another mode by which Canadian OI patients might be identified), a national surveillance program, such as the Canadian Paediatric Surveillance Program (CPSP), provides the only method by which the overall incidence of OI in Canada can be determined at the present time.

### **Anticipated significance and impact for patients**

Given the burden of this disease and the potential for significant amelioration with bisphosphonate therapy, it is important that the frequency and geographical distribution of OI be determined in Canada. By raising physicians' awareness of the disease through the distribution of case definitions, protocols, and resource materials, the CPSP will help to achieve a more timely diagnosis of new cases. This, in turn, will foster initiation of medical and supportive treatments during the critical years of bone growth and development, since the evidence to date shows that the largest benefit of bisphosphonate therapy occurs when it is initiated in the first few years of life. Education of paediatricians regarding OI in general and the novel forms in particular may also assist with the differentiation of an abused child from the child with bone fragility due to OI. By determining the geographic distribution of OI in Canada, the need for treatment programs in certain areas of the country may be identified. Furthermore, since the diagnosis of OI in childhood often leads to an unveiling of the condition in a parent or sibling, the identification of paediatric OI patients may result in appropriate



medical management for affected family members. Finally, the identification of novel OI forms (types V to VII) may facilitate the discovery of the underlying genetic basis of these OI types and assist physicians in their abilities to counsel families regarding prognosis and risk of disease transmission.

## **Methods**

The incidence of OI will be ascertained by determining all newly diagnosed cases in Canada over a one-year period (from January to December 2004 inclusively), through the CPSP. The CPSP is an established program that is designed to study uncommon childhood disorders, with high morbidity and mortality, and of such low frequency that national data collection is required to generate a sufficient number of cases for meaningful data.

Each month, participating physicians receive an initial reporting form asking them to indicate whether they have encountered a new case of OI in the preceding month. Once a participating paediatrician identifies a new case of OI, a detailed questionnaire, designed by the investigators, is sent requesting case-specific data.

## **Objectives**

### **Primary**

To determine the incidence of OI in Canada by ascertaining all newly diagnosed cases over a one-year period.

### **Secondary**

1. To raise physician awareness in Canada regarding OI in general and the novel forms in particular, so that diagnoses of OI can be made in a timely fashion, and appropriate treatment can be initiated during the critical years of bone growth and development.
2. To identify patients and/or kindreds with novel OI forms (OI types V to VII), for whom the genetic basis is presently unknown, in order to obtain clinical and genetic information that may ultimately lead to mutation identification.
3. To determine whether a geographic distribution of OI exists, so that regions in need of a local OI intervention program (including medical, orthopedic and rehabilitative care) can be identified.
4. To educate medical health providers and child welfare workers regarding the heterogeneous manifestations of OI, with the aim of facilitating the differentiation of the abused child from the child with congenital bone fragility due to OI. This, in turn, may prevent or minimize false allegations of child abuse.



## ***Osteogenesis imperfecta (continued)***

### **Case definition**

Report any child up to and including 18 years of age with:

- a new diagnosis of OI, defined as a congenital bone fragility condition associated with low bone mass;

**and**

- clinical features in keeping with a diagnosis of OI types I-VII (see Table 1).

### **Exclusion criteria**

- Bone fragility due to other causes, including genetic disorders (e.g., Ehlers Danlos syndrome), iatrogens (steroids, methotrexate, coumadin, radiotherapy), neuromuscular disease, chronic illness, endocrinopathies, idiopathic juvenile osteoporosis.
- Fractures due to child abuse.

### **Duration**

January to December 2004 (renewable)

### **Expected number of cases**

Based on an annual birth rate in Canada of 400,000 and on the available estimates of OI incidence (1:20,000 to 1:60,000 live births), the expected number of new OI cases is 7 to 20 per year.

### **Ethical approval**

Shriners Hospital for Children, McGill University  
Children's Hospital of Eastern Ontario, University of Ottawa.

### **Data analysis and publication**

This epidemiological study will generate statistics, such as means and frequencies, that will lead to the description of the characteristics of OI patients in Canada and the geographic distribution of the disease. More precisely, this exercise of measurement will focus on, but is not limited to, the determination of the number of new patients over a one-year period, the severity of the disease (based on, for example, age of first fracture, frequency of fractures, presence of long bone deformity and ambulatory status), and the identification of OI kindreds.

Non-nominal data for each patient will be collected at the time the detailed questionnaire is completed by the participating paediatrician and returned to the investigators for interpretation and analysis.



The results of this project will be presented to paediatric colleagues, including those in the fields of metabolic bone, endocrinology, orthopedics, child protection and genetics, and to public health policy makers. Manuscripts will be submitted for publication in paediatric scientific journals. As a member of INoPSU (International Network of Paediatric Surveillance Units), the CPSP will link study investigators with colleagues in other countries undertaking a similar initiative. Finally, results will be presented to the members of the OI Foundation and to OI families.

### References

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**Table 1: Classification of OI according to Silience and Glorieux (see references)**

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**1. OI type I (mild)**

Low-trauma fractures  
Blue sclera  
Minimal long bone deformity  
Normal or near-normal stature  
May have dentinogenesis imperfecta

**2. OI type II (lethal)**

Intrauterine fractures  
Beading of the ribs  
Blue sclera  
Broad, short femora  
Respiratory distress  
Death in the perinatal period

***Osteogenesis imperfecta (continued)*****3. OI type III (severe)**

- Frequent low-trauma fractures
- Variable scleral hue
- Extreme short stature
- Severe limb deformity
- Scoliosis
- Triangular facies
- Frequent dentinogenesis imperfecta

**4. OI type IV (moderately severe)**

- Low-trauma fractures
- Variable scleral hue
- Moderate short stature
- Moderate limb deformity
- Scoliosis
- May have dentinogenesis imperfecta

**5. OI type V**

- Low-trauma fractures
- Normal sclera\*
- Calcification of the interosseous membrane of the forearm or leg
- Dense metaphyseal band beneath the growth plate
- Hypertrophic callus formation in response to fractures and/or intramedullary rodding
- Absence of dentinogenesis imperfecta

**6. OI type VI**

- Low trauma fractures
- Normal sclera\*
- Moderate elevation in alkaline phosphatase
- Looser zones (pseudofractures) on x-ray
- Absence of dentinogenesis imperfecta
- Absence of wormian bones
- Plus: Absence of rickets

**7. OI type VII**

- Low trauma fractures
- Normal sclera\*
- Absence of dentinogenesis imperfecta
- Coxa vara
- Rhizomelia (shortening of the proximal limb segments of the upper and lower extremities)

\* Normal sclera = white or slightly blue