Hip Dysplasia in Children With Osteogenesis Imperfecta: Association With Collagen Type I C-Propeptide Mutations

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An association has also been reported between hip dysplasia and disorders associated with ligamentous laxity, such as Down syndrome, Ehlers-Danlos syndrome, Larsen syndrome, and Marfan syndrome.11–13

Screening of infants for hip dysplasia prevents late presentation of this disorder with irreversible complications. Screening is done clinically by performing Ortolani and Barlow tests and by use of ultrasonography. The clinical screening for hip dysplasia in infants with OI often is not easy, however, because of femoral bone deformity and the risk of fractures in these patients. Reported femur fractures have occurred in children with OI after clinical testing for hip dysplasia.15 Although there is a case report that described the association of hip dysplasia with OI in 1969,16 no other reports or case series described the association with collagen type I C-propeptide mutation.

On the basis of this, we performed the present retrospective case series study to gather information on how best to screen for, diagnose, and treat hip dysplasia in patients with OI.

METHODS

After receiving institutional review board approval, we retrospectively reviewed the charts of all patients with a diagnosis of OI who were seen at Shriners Hospital for Children-Canada between 1999 and 2013 to identify patients who had a diagnosis of hip dysplasia. We extracted the clinical characteristics of patients with hip dysplasia from their charts. This included information about the genetic mutation that caused OI in these children. In addition, the screening, treatment, complications, duration of follow-up, and clinical outcomes of treating these dysplastic hips were reviewed. Moreover, radiographic evaluation of all patients was done, including the assessment of acetabular indices and assessment of the concentric reduction and the development of ossified femoral nucleus to exclude any vascular compromise to the femoral head (Table 1).

### Statistical Analysis

The results were reported with the use of descriptive statistics. Testing for statistical significance was not performed due to the small number of cases in this series.

### RESULTS

A total of 687 children with a diagnosis of OI were assessed at our center during the observation interval. Among these, 5 patients (4 boys, 1 girl) were diagnosed with hip dysplasia, affecting a total of 8 hips. Review of the genetic information revealed that in 4 of these 5 children (80%), OI was caused by mutations affecting the C-propeptide of the collagen type I α1 chain, no one of these patients is related to the others, whereas in the entire group of children with OI, C-propeptide mutations were present in a total of 26 patients. Thus, the prevalence of hip dysplasia was 0.87% (5 of 687) in the entire study cohort, but 15% (4 of 26) among patients with C-propeptide mutations.

The diagnosis of hip dysplasia had been made between 3 weeks and 27 months of age (mean: 13.9 mo). Early clinical screening failed to diagnose hip dysplasia in all cases except 1. Pavlik harness treatment was used in 2 children but failed. All patients underwent surgical treatment, including either a closed or an open reduction and a femoral osteotomy. Four hips had closed reduction with a femoral osteotomy. Open reduction with a femoral osteotomy was performed in 4 hips and pelvic osteotomy was performed in 2 hips. There was 1 case of redislocation after an open reduction and 1 case of osteonecrosis of the femoral head after treatment with a Pavlik harness. The range of follow-up duration was 8 months to 9 years with an average of 3.4 years.

### TABLE 1. Patient Demographics and Results

| Case | Sex | Type of OI | Mutation | Age at Diagnosis | Side | Age at Surgery | Complications | Duration of Follow-up | Initial Acetabular Index | Final Acetabular Index | Postoperative Function |
|------|-----|-----------|----------|-----------------|------|----------------|---------------|-----------------------|--------------------------|------------------------|------------------------|
| 1    | M   | III       | COL1A1   | c.4325T>G p.Val1442Gly | 3 wk | Bilateral (L) hip at 23 mo | Left femoral head AVN after Pavlik harness | 6 y | (R) 27, (L) 30 | (R) 19, (L) 20 | Active, plays soccer and basket ball Walking independently without aids Still on abduction brace at night |
| 2    | F   | III       | COL1A1   | c.4274C>T p.Thr1425>Ile | 8 mo | Bilateral (L) at 3 y. (R) at 6.3 y | None | (R) 18 mo, (L) 4 y | (R) 37, (L) 34 | (R) 24, (L) 22 |
| 3    | M   | III       | COL1A1   | c.3895T>C p.Cys1299Arg | 10 mo | Right | 19 mo | Redislocation | 14 mo | (R) 32, (L) 25 | (R) 29, (L) 20 |
| 4    | M   | IV        | COL1A1   | c.1072G>A p.Gly358Ser | 24 mo | Right | 27 mo | None | 9 y | (R) 31 | (R) 17 | Transfers by himself and able to swim Walking independently without aids |
| 5    | M   | IV        | COL1A1   | c.4239_4237del p.1410_1412del | 27 mo | Bilateral | 28 mo | None | 8 mo | (R) 33, (L) 28 | (R) 23, (L) 22 | Walking independently without aids |

The mutation information indicates the gene, the nucleotide change, and the amino acid change caused by the nucleotide change. C-propeptide mutations are shown in bold print.

AVN indicates avascular necrosis; F, female; (L), left; M, male; OI, osteogenesis imperfect; (R), right.
Case 1

This boy presented to the OI team at the age of 7 months. He was born by spontaneous vaginal delivery in a breech presentation following an uneventful pregnancy. His mother did not notice any intrauterine movements at all during her pregnancy. There was no family history of OI or hip dysplasia. At birth, asymmetric movements of the lower limbs were noted. He was diagnosed with OI at another institution. At 3 weeks of age, bilateral hip dysplasia was diagnosed at that institution and the patient was treated with a Pavlik harness. When the harness was put on, fractures of both femurs, the proximal left tibia, and the proximal right fibula were noted. The decision at that time was to do nothing about the hip dysplasia until the femur fractures had healed, to keep the Pavlik harness, and to start bisphosphonate infusion. Closed reduction and hip spica cast application were not chosen because these can lead to further osteopenia. The plan was rather to perform an open reduction at the same time as femoral osteotomy and rodding. Although we recommended removal of the Pavlik harness, it was continued by the other institution. The patient was seen again in our institution at the age of 13 months with a failed Pavlik harness treatment. The x-ray showed bilateral hip dysplasia and signs of type I bilateral avascular necrosis according to Kalamchi and McEwen’s classification, which was confirmed by magnetic resonance imaging. When he started walking at the age of 23 months, the patient underwent left hip open reduction, femoral shortening osteotomy, and telescoping rodding and a hip spica was applied for 6 weeks. The concentricity of reduction was confirmed by a computed tomography scan. One year later, closed reduction femoral osteotomy and telescoping rodding were performed on the right side. The x-ray of both hips showed that both hips are reduced and well developed (Fig. 1).

Case 2

This girl was born at term, and diagnosed with OI after birth because of multiple fractures. Bilateral hip dysplasia was diagnosed at 8 months of age. Because of ligamentous laxity and ability to reduce the hip initial treatment started with a Pavlik harness application for 3 months, which failed to keep both hips reduced. At the age of 3 years, open reduction of the left hip, Salter osteotomy, femoral varus derotational osteotomy, and telescoping rodding and a hip spica was applied for 6 weeks. The concentricity of reduction was confirmed by a computed tomography scan. One year later, closed reduction femoral osteotomy and telescoping rodding were performed on the right side. The x-ray of both hips showed that both hips are reduced and well developed (Fig. 1).

Case 3

OI was diagnosed at birth for this boy. Right hip dysplasia was diagnosed at the age of 10 months. Treatment of the right hip was done at the age of 19 months by an open reduction, femoral osteotomies, and insertion of telescopic rods in both femurs. At the age of 23 months,
the patient started to stand, and his right hip appeared dislocated on the x-ray. A night abduction brace was applied until his scheduled revision surgery.

Case 4

A clinical diagnosis of OI at birth of this boy was made and genetic testing revealed a glycine mutation in the triple helical part of the COL1A2 gene (Table 1). Thus, this is the only patient in the present series who does not have a C-propeptide mutation. Right hip dysplasia was diagnosed at the age of 24 months and was treated initially by closed reduction, left femoral osteotomy, and telescoping rods. Three months after surgery, the patient started walking and radiographs of both hips showed that both femoral heads were located in the acetabulum, with no evidence of avascular necrosis.

Case 5

OI was diagnosed after this boy was born at term because of multiple fractures. Dysplasia of both hips was noted at the age of 27 months and was treated by closed reduction, varus femoral osteotomy, and telescoping rods. Three months after surgery, the patient started walking and radiographs of both hips showed that both femoral heads were located in the acetabulum, with no evidence of avascular necrosis.

DISCUSSION

In this study, we found that 5 out of 687 children with OI had hip dysplasia. There is no known cause for hip dysplasia, although there are associated risk factors such as female sex, first born, breech presentation, and ligamentous laxity. A C-propeptide mutation was present in 26 of the 687 children with OI. Four of the 5 children diagnosed with hip dysplasia concomitant with OI (80%) had a confirmed C-propeptide mutation. The mechanistic link between C-propeptide mutations and hip dysplasia is not clear at present. However, these results show that patients with C-propeptide mutations need to be carefully assessed for hip dysplasia, particularly if the newborn is delivered in a breech presentation and/or the presence of a femur recurvatum (Fig. 2). To our knowledge, no case series have previously been published describing the association of hip dysplasia with OI in children. However, 2 cases in siblings have been reported.\(^\text{16}\) The prevalence of hip dysplasia in our series of patients is therefore 7 per 1000, which is higher than the prevalence in the general population (0.7 to 1.2 per 1000 live births).\(^\text{9,18,19}\) Spoon- seller et al\(^\text{13}\) reported an incidence of hip dysplasia of 2% in association with Marfan syndrome. Our case series included 4 boys (80%) and only 1 girl (20%), which is in contrast with the female predominance for hip dysplasia (81% female predominance) in the general population.\(^\text{20}\)

Hip dysplasia was diagnosed late in 4 children because of the rarity of this association and fear of causing a fracture during clinical examination, as reported in a case series in which fractures of the femur occurred during testing for hip dysplasia.\(^\text{15}\) Clinical examination was difficult in these children because of the deformed femur; hyperlaxity, which results in full abduction with clinical examination; and the presence of other conditions such as club feet, which was treated in 1 child by the Ponseti method before the hip dysplasia was diagnosed. Treatment with a Pavlik harness was attempted in 2 patients but was not effective in either case. One case in which the harness was applied for 6 months had osteonecrosis of the femoral head, which was confirmed by magnetic resonance imaging. Because of the rarity of the condition, we could not find ultrasound classification in the charts, and we were not able to classify the starting severity and if any improvement was noted, however, this is an area for further research. The unsuccessful results of the harness may be related to the ligamentous laxity or the femoral bone deformity, late application, and the presence of fractures. The reported failure rate of treatment of frank hip dislocation in children with a Pavlik harness is 25%.\(^\text{21}\) Closed reduction was reported to be successful for treating hip dysplasia in a series of 4 children with hip dysplasia associated with Marfan syndrome.\(^\text{13}\) The surgical treatment of hip dysplasia in children older than 18 months is redirectional femoral osteotomies and acetabular osteotomies, but in younger children the surgical treatment is adductor tenotomy and closed reduction versus open reduction often without osteotomies.\(^\text{22}\) In our series, we think that the associated femoral deformity and fractures in the OI patients made the concentric reduction more difficult and a femoral varus derotational shortening osteotomy was the key to maintaining a concentric reduction and not a pelvic osteotomy. We had to use concomitant pelvic osteotomies in 2 hips (1 patient) only because of the significant acetabular dysplasia. All acetabular indices have gone back to normal except for

![FIGURE 2. Anteroposterior view of both hips and femurs at 24 months of age; on the left side the typical procurvatum deformity of the femur, and on the right side the recurvatum due to the breech presentation.](image-url)
the third case (29 degrees). He is on an abduction brace and scheduled for revision of open reduction of the dislocated hip.

**CONCLUSIONS**

About 80% of OI patients with hip dysplasia are associated with C-propeptide mutation. Clinical screening for hip dysplasia is difficult in OI patients owing to bowing of the proximal femur and the risk of causing fractures. Therefore, all OI children with positive C-propeptide mutation should be screened for hip dysplasia with ultrasound. We did not find any role for the Pavlik harness in treating hip dysplasia in OI children. Management was achieved by a femoral osteotomy with either closed or open reduction of the hips with or without concomitant pelvic osteotomy.

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