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

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Background: Osteogenesis imperfecta (OI) is a heritable skeletal disorder characterized by bone fragility and short stature that is usually due to mutations in 1 of the 2 genes that code for collagen type I α-chains. The association between hip dysplasia and OI has not been systematically investigated. In this single-center study, we retrospectively reviewed all cases of OI associated with hip dysplasia to describe clinical characteristics and the effect of therapy.

Methods: We reviewed the charts of 687 patients with OI who were seen at the Shriners Hospital for Children in Montreal between 1999 and 2013 to identify patients with a diagnosis of hip dysplasia. Clinical characteristics and the course after therapeutic interventions were extracted from the charts.

Results: Hip dysplasia was diagnosed in 8 hips of 5 patients (4 boys, 1 girl; age at diagnosis ranged between 3 wk and 27 mo old). The prevalence of hip dysplasia and OI was therefore 0.87% (per patient). In 4 of the 5 patients (80%), OI was caused by mutations affecting the C-propeptide of collagen type I, which is otherwise rare in OI. Among the 26 patients with C-propeptide mutations followed at our institution, 4 (15%) had hip dysplasia. Pavlik harness treatment was attempted in 2 patients (3 hips) but was not effective in either case and resulted in avascular necrosis of 1 hip. Femoral varus derotational shortening osteotomies using a telescopic rod were performed in all 8 hips along with a closed reduction in 4 hips and an open reduction in 4 hips. Concomitant pelvic osteotomies were performed in 2 hips (1 patient). Surgery resulted in redislocation of 1 hip; all other surgically treated hips remained reduced.

Conclusions: Clinical screening for hip dysplasia is difficult in OI owing to the bowing of the proximal femur and the risk of causing fractures. OI patients with positive C-propeptide mutation should therefore be screened for hip dysplasia by use of ultrasound. Presence of a C-propeptide mutation appears to be a risk factor for hip dysplasia (80%). It appears that Pavlik harness treatment is not useful in children with OI. The usual treatment of children with OI who pull to stand or started walking with femoral deformity is femoral osteotomy and rodding. In case of associated hip dysplasia with a dislocation, open reduction of the hip and a possible concomitant pelvic osteotomy appears to be a valid management option.

Level of Evidence: Level IV.

Key Words: collagen type I C-propeptide, developmental dysplasia, hip dysplasia, mutation, osteogenesis imperfecta

(*J Pediatr Orthop* 2017;37:479–483)

Osteogenesis imperfecta (OI) is a genetically determined disorder of connective tissue characterized by bone fragility, deformities of long bones, and short stature.[1,2] Ekman provided the first scientific description of OI in 1788, but it was not until 1849 that Vrolik coined the term to describe the condition.[3] OI affects up to 1/10,000 individuals of all racial and ethnic origins.[4,5]

OI is characterized by decreased bone quality and quantity and variable bone deformities secondary to either decreased or abnormally produced collagen. The majority of patients have a mutation in either the *COL1A1* or the *COL1A2* gene,[6,7] the 2 genes coding for the α-1 and α-2 chains of collagen type I, respectively.[8] Collagen type I is a heterotrimer consisting of 2 α-1 chains and 1 α-2 chain. It is initially synthesized as a pro-α chain with a propeptide at each end (N-propeptide and C-propeptide). The C-propeptide is necessary for pro-α chain association and triple helix formation, which starts at the C-terminal propeptide and extends to the N-terminal propeptide in a zipper-like manner.[8]

The prevalence of hip dysplasia in the general population is 0.7 to 1.2 per 1000 births.[9] The predisposing risk factors for hip dysplasia are a positive family history, perinatal breech positioning, and ligamentous laxity.[10]

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None of the authors received financial support for this study.

M.G. is a consultant for smith and nephew, and issued a patent from Pega medical. F.R. recieved grants from The Canadian Institutes of Health Research. The other authors declare no conflicts of interest.

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DOI: 10.1097/BPO.0000000000000644

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.[10,14] 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 α-1 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
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	Walking independently without aids
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	Still on abduction brace at night
4	M	IV	***COL1A2*** c.1072G > A p.Gly358Ser	24 mo	Right	27 mo	None	9 y	(R) 31	(R) 17	Transfers by himself and able to swim
5	M	IV	***COL1A1*** c.4229_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.

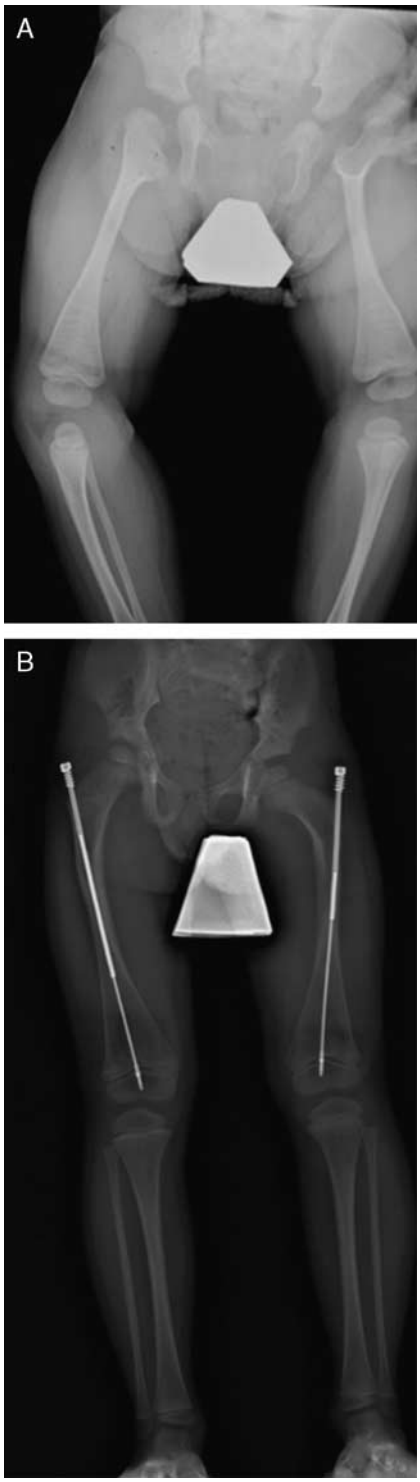

FIGURE 1. A, X-ray of both hips at 18 months of age showing a bilateral hip dislocation. B, Final x-ray showing healed osteotomy sites with concentrically reduced hips with no signs of avascular necrosis.

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[17] 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 telescopic rodding of the left femur were performed. At the age of 6 years, closed reduction of the right hip, femoral varus derotational osteotomy, telescopic rodding of the right femur, and a Dega osteotomy of the right hip were performed. The treatment of the right hip was delayed as the patient came from another country. At the age of 7 years, the patient was able to walk without any aid, and both hips were reduced and stable clinically and radiologically.

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 osteotomies, and a telescoping rodding. The right hip failed to reduce. Three weeks later, the patient underwent open reduction of the right hip, femoral osteotomies, and insertion of a telescoping rod in the right femur. X-rays of both hips showed that the right femoral head is still located in the acetabulum.

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.[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).[9,18,19] Sponseller et al[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.[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.[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%.[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.[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.[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

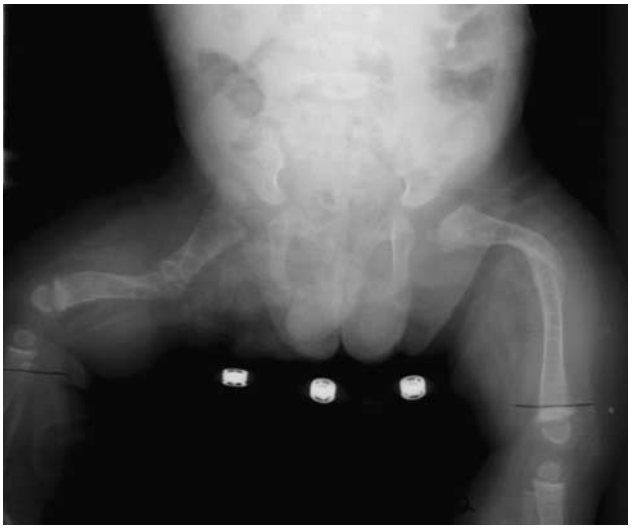

FIGURE 2. Anteroposterior view of both hips and femurs at 24 months of age; on the left side the typical procurvatum deformity of the femur, and on the right side the recurvatum due to the breech presentation.

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.

REFERENCES

1. Kocher MS, Shapiro F. Osteogenesis imperfecta. *J Am Acad Orthop Surg*. 1998;6:225–236.
2. Forlino A, Cabral WA, Barnes AM, et al. New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol*. 2011;7:540–557.
3. Burnei G, Vlad C, Georgescu I, et al. Osteogenesis imperfecta: diagnosis and treatment. *J Am Acad Orthop Surg*. 2008;16:356–366.
4. Byers PH, Steiner RD. Osteogenesis imperfecta. *Annu Rev Med*. 1992;43:269–282.
5. Glorieux FH. Osteogenesis imperfecta. *Best Pract Res Clin Rheumatol*. 2008;22:85–100.
6. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet*. 2004; 363:1377–1385.
7. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet*. 1979;16:101–116.
8. Ben Amor IM, Glorieux FH, Rauch F. Genotype-phenotype correlations in autosomal dominant osteogenesis imperfecta. *J Osteoporosis*. 2011;2011:540178.
9. Randall T, Loder ENS. The epidemiology and demographics of hip dysplasia. *ISRN Orthopaedics*. 2011;2011:238607–238646.
10. Guille JT, Pizzutillo PD, MacEwen GD. Development dysplasia of the hip from birth to six months. *J Am Acad Orthop Surg*. 2000;8:232–242.
11. Laville JM, Lakermance P, Limouzy F. Larsen's syndrome: review of the literature and analysis of thirty-eight cases. *J Pediatr Orthop*. 1994;14:63–73.
12. Sankar WN, Schoenecker JG, Mayfield ME, et al. Acetabular retroversion in Down syndrome. *J Pediatr Orthop*. 2012;32:277–281.
13. Sponseller PD, Tomek IM, Pyertiz RE. Developmental dysplasia of the hip in Marfan syndrome. *J Pediatr Orthop B*. 1997;6:255–259.
14. Moss GD, Cartlidge PH, Speidel BD, et al. Routine examination in the neonatal period. *BMJ*. 1991;302:878–879.
15. Paterson CR, Beal RJ, Dent JA. Osteogenesis imperfecta: fractures of the femur when testing for congenital dislocation of the hip. *BMJ*. 1992;305:464–466.
16. du Toit SN, Weiss C. Congenital dislocation of hips associated with osteogenesis imperfecta in male siblings. A case report. *Bull Hosp Joint Dis*. 1969;30:164–170.
17. Kalamchi A, McEwen GD. Avascular necrosis following treatment of congenital dislocation of the hip. *J Bone Joint Surg*. 1980;62-A:876–887.
18. Burke SW, Macey TI, Roberts JM, et al. Congenital dislocation of the hip in the American black. *Clin Orthop Relat Res*. 1985;192:120–123.
19. Gross RH, Wisnefske M, Howard TC III, et al. The Otto Aufranc Award Paper. Infant hip screening. *Hip*. 1982;T:50–67.
20. Hazel JR, Beals RK. Diagnosing dislocation of the hip in infancy. *West J Med*. 1989;151:39–41.
21. Tredwell SJ, Bell HM. Efficacy of neonatal hip examination. *J Pediatr Orthoped*. 1981;1:61–65.
22. Gillingham BL, Sanchez AA, Wenger DR. Pelvic osteotomies for the treatment of hip dysplasia in children and young adults. *J Am Acad Orthop Surg*. 1999;7:325–337.