Osteogenesis Imperfecta Type III With Intracranial Hemorrhage and Brachydactyly Associated With Mutations in Exon 49 of COL1A2

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Osteogenesis imperfecta (OI) is a heritable bone disorder characterized by fractures with minimal trauma. Intracranial hemorrhage has been reported in a small number of OI patients. Here we describe three patients, a boy (aged 15 years) and two girls (aged 17 and 7 years) with OI type III who suffered intracranial hemorrhage and in addition had brachydactyly and nail hypoplasia. In all of these patients, OI was caused by glycine mutations affecting exon 49 of the COL1A2 gene, which codes for the most carboxy-terminal part of the triple-helical domain of the collagen type I alpha 2 chain. These observations suggest that mutations in this region of the collagen type I alpha 2 chain carry a high risk of abnormal limb development and intracranial bleeding.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable bone disorder characterized by fractures with minimal trauma, dentinogenesis imperfecta, and, in adult years, hearing loss. The clinical spectrum represents a continuum ranging from perinatal lethality to nearly asymptomatic individuals with occasional fractures and normal stature [Rauch and Glorieux, 2004].

The majority of individuals with a clinical diagnosis of OI have an identifiable mutation in either COL1A1 or COL1A2, the genes that code for collagen type I alpha chains [Rauch and Glorieux, 2004]. These alpha chains contain a glycine residue at every third position of their triple-helical domains. Glycine residues are essential for the alpha chains to intertwine correctly and for the assembly of collagen fibrils. The most common mutations in OI types II, III, and IV result in the substitution of glycine by another amino acid in the triple-helical domain of either alpha chain. A large number of such mutations have been identified in OI patients, but it remains difficult to establish correlations between a specific genotype and the resulting phenotype [Marini et al., 2007].

Intracranial hemorrhage has been reported in a small number of OI patients [Pozzati et al., 1983; Diaz and Lippe, 1985; Sayre et al., 1987; Knisely et al., 1988; Tokoro et al., 1988; Cole and Lam, 1996; Groninger et al., 2005; Parmar et al., 2007]. Here we describe three patients with OI type III who suffered subdural hematoma and in addition had short limbs as well as marked digital and nail hypoplasia. In all patients, OI was caused by glycine mutations affecting the most carboxy-terminal part of the triple-helical domain of the collagen type I alpha 2 chain, α2(I).

PATIENTS AND METHODS

Patients

The patients described in this report are part of a cohort of about 400 patients with OI who have been examined at the Shriners Hospital for Children in Montreal over the past 5 years. For the purpose of this publication, informed consent was obtained from legal guardians and patients.

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Collagen Type I Mutation Analysis

Genomic DNA from peripheral blood leukocytes was analyzed using the methodology described by Korkko et al. [1998]. All exons of the COL1A1 and COL1A2 genes and their respective exon—intron boundaries, with the exception of the six exons encoding the N-propeptides, were amplified by polymerase chain reaction. Polymerase chain reaction products were screened for mutations by conformation-sensitive gel electrophoresis [Ganguly et al., 1993]. Those products containing heteroduplexes were then sequenced using the ThermoSequenase® kit (Amersham, Cleveland, OH).

CLINICAL REPORTS

Patient 1

This girl was born at term by cesarean with a weight of 2,440 g and a length of 45.7 cm (both at 5th centile). The parents were not consanguineous and there was no family history of bone diseases, intracranial hemorrhage, or digital anomalies. Multiple fractures of ribs and long bone were noted as well as shortness of upper and lower limbs. There was bilateral mesomelia and significant hypoplasia of all digits and nails. A diagnosis of OI type III was made. Nucleotide sequencing studies revealed a point mutation in exon 49 of the COL1A2 gene leading to the substitution of glycine at position 1090 of α2(I) by aspartic acid.

At 7 years of age, lumbar spine bone mineral density was below the result expected for newborns. She had more than 30 fractures in a period of 1 year. Bisphosphonate treatment was started (cyclical intravenous pamidronate for 1 year; thereafter alendronate given orally once weekly when venous access became difficult) and was maintained until the age of 15 years.

At 15 years of age, she was diagnosed to have left parietal subdural hematoma without history of preceding trauma. The subdural hematoma was evacuated and the patient recovered without neurological impairment.

The last follow-up at age 17 years revealed extremely short stature (96.9 cm, 54 cm below the 5th centile for age) and severe obesity (61 kg, 75th centile for age). The head was large (56 cm, 95th centile for age) with frontal bossing. She had severe dentinogenesis imperfecta. The patient had rhizo-meso-acromelia with significantly hypermobile joints and loose skin, especially around fingers (Fig. 1). Radiographs of hands and feet showed severe shortening and thinning of all tubular bones including metacarpal and metatarsal bones. The shortening was especially marked at the distal phalanges.

Patient 2

This boy was born at term by cesarean. Birth weight was 3,770 g (50th centile), birth length was not documented. Multiple fractures involving long bones and ribs as well as deformities of upper and lower extremities were noted at birth. The parents were not consanguineous and there was no family history of bone diseases, intracranial hemorrhage, or digital anomalies. A diagnosis of OI type III was made. Subsequently, nucleotide sequencing studies revealed a point mutation in exon 49 of the COL1A2 gene, which predicted the substitution of glycine at position 1096 of α2(I) by alanine. At the age of 4 months, a large arachnoid cyst and bilateral subdural hematoma were detected for which he underwent surgical evacuation and shunting. No further bleeding episodes occurred thereafter and neurological recovery was complete. Nevertheless, the boy continued to suffer from a high fracture frequency throughout early childhood, which severely impaired his mobility.

At 6 years of age, lumbar spine areal bone mineral density was below the result expected for newborns. Transiliac bone biopsy demonstrated the typical histological picture of severe OI (low amount of cortical and trabecular bone; abnormally large number of osteocytes; elevated bone turnover). Treatment with cyclical intravenous pamidronate was started and was maintained until the age of 11 years.

At the time of last follow-up at 15 years of age, patient 2 was extremely short (108 cm, 48 cm below the 5th centile for age) with a weight of 50 kg (25th centile for age). His head was relatively large (head circumference 58 cm, corresponding to the 95th centile for age) with prognathism. He used a motorized wheelchair for mobility and had mild scoliosis (10°) as well as upper and lower limb deformities. He had small hands and feet. The fingers and toes were short with hypoplastic nails (Fig. 2). Radiographs of hands and feet showed short and broad metacarpals and metatarsals as well as short phalangeal bones with hypoplastic distal phalanges.

FIG. 1. Patient 1 at the age of 17 years. Acromelia and hypoplastic nails are visible in hands (A,B) and feet (C,D). Phalanges are short with thin diaphyses and wide metaphyses. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Patient 3

This girl had been diagnosed with OI in utero, after ultrasound examinations had revealed the presence of short and deformed limbs. She was born by cesarean after 37 weeks of gestation. Birth weight was 1.72 kg, length 37 cm and head circumference 30 cm (all measures were below the 5th centile for gestational age). The parents are not consanguineous and their family histories were negative for bone and bleeding disorders. Radiographs revealed numerous lower and upper extremity fractures in addition to Wormian bones. Nucleotide sequencing studies revealed a point mutation in exon 49 of the \textit{COL1A2} gene leading to the substitution of glycine at position 1099 of \(\alpha_2(1)\) by arginine.

Cyclical intravenous pamidronate therapy was initiated at 2 months of age. At 6.5 years of age, she fell from her wheelchair and subsequently developed severe headache and vomiting. Computed tomography of the brain showed epidural hematoma (Fig. 3). She underwent urgent craniotomy and evacuation of the blood collection. At the time of last follow-up (age 6.8 years), she was very short (height 74.5 cm; 34 cm below the 5th centile for age), and had short and small hands, fingers, and toes. The hand radiograph showed broad and short phalangeal bones (Fig. 4).
DISCUSSION

Here we describe three patients who not only had typical skeletal manifestations of OI type III but also had brachydactyly and suffered from intracranial hemorrhage. In all patients, OI was caused by mutations in exon 49 of the COL1A2 gene, predicting glycine substitutions in the most carboxy-terminal segment of the a2(I) triple-helical domain.

To our knowledge, the particular constellation of clinical features that we observed in the present patients has not been previously described in OI. Patient 1 had been reported in his infancy as having arachnoid cyst and subdural hematoma, but the digital findings were not mentioned [Cole and Lam, 1996]. The published literature on intracranial bleeding in OI patients is limited to a few case reports [Pozzati et al., 1983; Diaz and Lippe, 1985; Sayre et al., 1987; Knisely et al., 1988; Tokoro et al., 1988; Cole and Lam, 1996; Groninger et al., 2005; Parmar et al., 2007]. During the past 5 years, we have examined ~400 OI patients below 18 years of age, four of whom had a history of intracranial bleeding. This corresponds to a prevalence of about 1% for intracranial bleeding in the pediatric OI population. Apart from the three patients described here, a girl with OI type I (due to a nonsense mutation in COL1A1) suffered intracerebral bleeding at the age of 14 years (unpublished observation). However, in her case magnetic resonance imaging revealed the presence of moyamoya disease as a causative factor.

Brachydactyly is not usually a feature of OI. It is true that shortness of tubular bones is one of the typical characteristics of OI, especially in the lower extremities. In many cases, this may be explained by frequent fractures that interfere with growth plate activity or even destroy growth plates, leading to the radiological picture of “popcorn epiphyses.” However, it is very unlikely that the marked shortness of the phalanges in our patients was due to fractures. There was no history of repeated finger fractures and all fingers appeared to be affected in a similar manner. It is more plausible to assume that brachydactyly was caused by a more direct effect of the COL1A2 mutations on bone growth. The mechanism of such an effect is unclear at present.

The three patients described here not only share a history of intracranial bleeding and a similar phenotype but also had mutations in exon 49 of the COL1A2 gene that affected closely spaced glycine residues (Fig. 5). These glycine residues are located at the C-terminal end of the triple-helical domain of a2(I). Over the past 5 years we have examined 153 other OI patients who had mutations causing glycine substitutions in collagen type I (54 in COL1A1, 92 in COL1A2), but none of these had a history of intracranial bleeding or brachydactyly. Our observations therefore suggest that brachydactyly and a predisposition to intracranial bleeding are rather specific to the mutations described here.

At present there is no obvious mechanistic explanation for a functional link between these COL1A2 exon 49 mutations, brachydactyly and intracranial bleeding. It is also unclear whether substitutions of these glycine residues by amino acids other than the ones found in our patients or mutations in adjacent glycine residues may result in a similar phenotype. Recent compilations of COL1A2 mutations mention other patients who have mutations affecting these same glycine residues as well as glycine residues that are caused by mutations affecting exon 48 of COL1A2 [Pollitt et al., 2006; Marini et al., 2007]. However, these reports did not provide phenotypic descriptions. We are following another OI patient who has a mutation in the most C-terminal glycine residue of the a2(I) triple-helical domain (Gly1102 > Arg, the mutated glycine residue is indicated by an asterisk in Fig. 5) but has a markedly different phenotype. He is diagnosed with OI type IV, has normal height (5th centile for age), normal fingers and toes, and has not had intracranial bleeding.

In conclusion, the observations made in these three patients suggest that at least some glycine mutations in the C-terminal part of the collagen type I alpha 2 triple helix lead to abnormal limb development and carry a high risk of intracranial bleeding.

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