The first case of Bruck syndrome associated with gastroschisis

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SUMMARY: Afşarlar ÇE, Peltek-Kendirci HN, Erdoğan D, Özgüner İF, Çavuşoğlu YH, Karaman A, Çetinkaya S. The first case of Bruck syndrome associated with gastroschisis. Turk J Pediatr 2013; 55: 651-654.

Bruck syndrome is an extremely rare disorder featuring the unusual combination of skeletal changes resembling osteogenesis imperfecta with congenital contractures of large joints. Although the genotypic and phenotypic features of Bruck syndrome are heterogeneous, we report a baby girl having gastroschisis complicated with jejunal perforation in addition to bone fractures and joint contractures, which supported the diagnosis of Bruck syndrome. After surgical procedures for gastroschisis, the fractures were treated with splints, and cyclic pamidronate treatment was started. On postoperative day 30, the patient was discharged without any complications. She is now seven months of age, gaining weight and has had no additional fractures with the ongoing pamidronate treatment. Although prematurity and low birth weight are common in gastroschisis, musculoskeletal anomalies have not been reported until now, and thus the case is unique. Additionally, cyclic pamidronate administration is a good treatment choice for bone fragility in Bruck syndrome to reduce the number of fractures, and it may be beneficial for the subsequent clinical deterioration of the patients.

Key words: Bruck syndrome, gastroschisis, osteogenesis imperfecta, joint contracture, pamidronate.

Bruck syndrome (BS) is a rare disorder featuring the unusual combination of skeletal changes resembling osteogenesis imperfecta (OI) with congenital contractures of large joints. Since Bruck identified this disorder in 1897 and Viljoen et al.[1] defined the syndrome in 1989, a limited number of patients have been reported in the English-language literature[1]. The hallmarks of BS are bone fragility associated with the unusual finding of pterygia and contractures of the large joints. The genotypic and phenotypic features of BS are heterogeneous; however, recent studies have demonstrated recessive mutations in the *PLOD2* and *FKBP10* genes[2,3]. Until now, none of the reported cases had associated anomalies outside of the musculoskeletal system. This is the first case of BS with gastroschisis.

Case Report

A female baby with a prenatal diagnosis of gastroschisis was delivered in our hospital by cesarean section at the 36th gestational week because of fetal distress, with a birth weight of 1350 g. Her mother was 19 years old and healthy. Subsequently, the patient was transported to our pediatric surgery department. On physical examination, she had gastroschisis complicated with jejunal perforation and type 2 jejunal atresia. Furthermore, she had contractures and pterygia at the elbows, hips, and knees and club foot bilaterally (Fig. 1). She had a crepitating, tender swelling on the left femur, and X-ray study revealed a left femur fracture (Fig. 2). An emergency operation was performed, including resection of the 20 cm necrotic perforated jejunum beginning from the ligament of Treitz and ending at the site of the type 2 atresia, primary end-to-end anastomosis and reduction of the bowel segments into the abdominal cavity. On postoperative day 3, she had an additional fracture on the left humerus (Fig. 3); both fractures were followed with splints and recovered with callus formation (Fig. 4). Wormian bones were demonstrated in the scull X-ray (Fig. 5). She tolerated

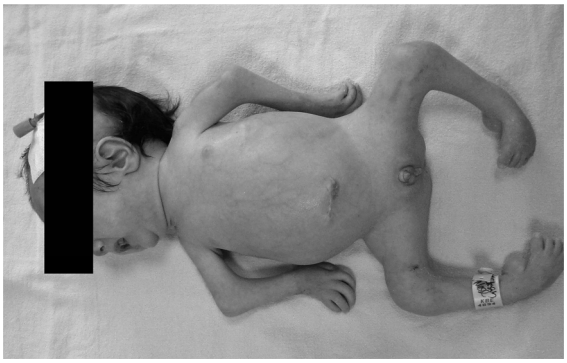

Fig. 1. Photograph on postoperative day 30 demonstrating abdominal wall closure scar, both the upper and lower limb contractures with pterygia, and club feet.

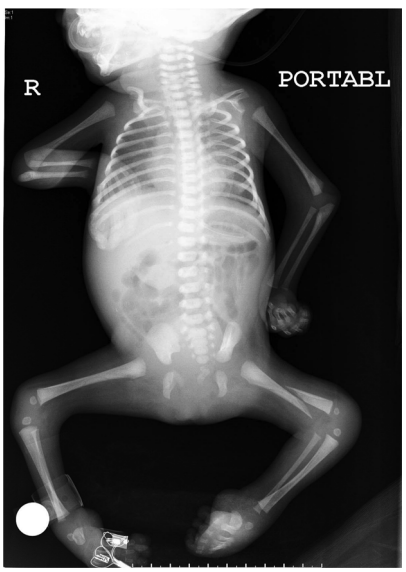

Fig. 2. X-ray image demonstrating left femur fracture.

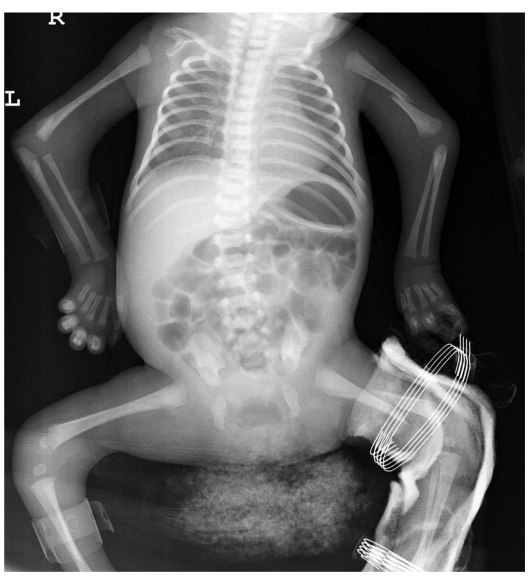

Fig. 3. X-ray image demonstrating the new fracture on the left humerus and splint of the left femur.

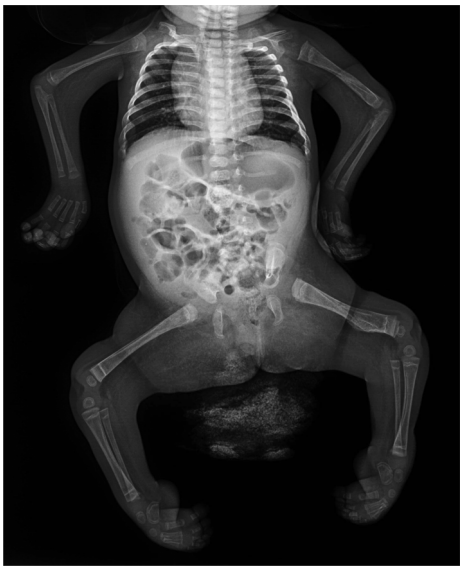

Fig. 4. X-ray image demonstrating callus formation in the left femur and humerus.

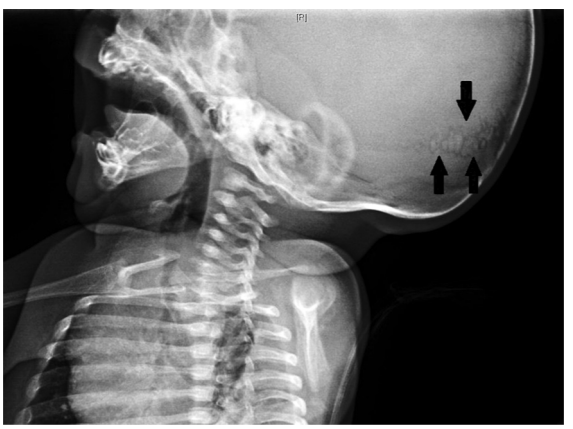

Fig. 5. Arrows demonstrate the Wormian bones on skull X-ray.

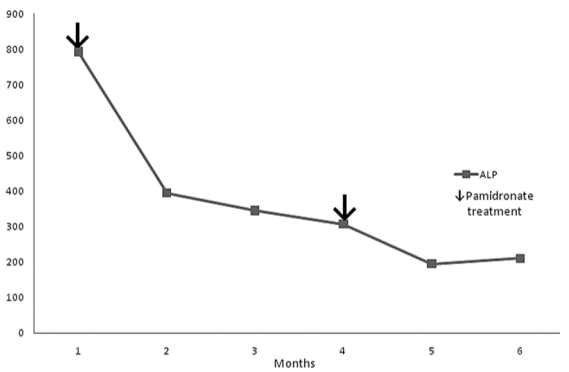

Fig. 6. Alkaline phosphatase (ALP) levels during pamidronate treatment.

oral feeding within postoperative day 9. The presence of the congenital joint contractures in addition to multiple bone fractures promoted the diagnosis of BS. After reaching a weight of 2000 g at postnatal day 30, initial treatment of pamidronate disodium (Aredia; Novartis Pharma Stein AG, Switzerland) was given in 1 hour infusion at a dosage of 0.5 mg/kg/day in 100 ml saline solution for two days. Elementary calcium (50 mg/kg/day in divided doses) and vitamin D (400 U/day) were also given orally. She was discharged without any side effect after pamidronate treatment. Cyclic pamidronate treatment was given in a period of three months. Complete blood count, renal and liver functions, and calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) levels were checked in every cycle. The ALP was found to be decreased on follow-up (Fig. 6). The levels of ALP were 794 U/L and 210 U/L at 1 and 7 months of age, respectively (reference range of ALP for infancy: 60-321 U/L). After the second cycle of pamidronate treatment, bone mineral densitometry (BMD) of the lumbar spine (L1-L4) was measured as 0.408 g/cm^2 on dual-energy X-ray absorptiometry (Hologic QDR 4500A; Hologic Inc., Bedford, MA, USA). She is now 8 months of age, gaining weight without any gastrointestinal complaints, and has not experienced any additional fractures with the ongoing pamidronate treatment.

Discussion

Gastroschisis is one of the congenital abdominal wall defects, with an incidence of 2 to 4.9 per 10,000 live births, and it has a male predominance. The etiology of gastroschisis is unclear, but the early resorption of the right umbilical vein at about 4 weeks' of gestation, leading to umbilical coelom failure, is commonly blamed for the development of gastroschisis[4]. The anomalies associated with gastroschisis are usually related to the midgut, with the most common being intestinal atresia, which was encountered in our patient. Moreover, prematurity and low birth weight, as demonstrated in our patient, are the other common associations[4]. Association of a musculoskeletal system disorder with gastroschisis has not been reported until this case.

Bruck syndrome (BS) is a rare disorder that resembles OI with the presence of bone fragility but differs with the existence of joint contractures and pterygia at birth. Furthermore, in contrast to OI, absence of hearing loss and dentinogenesis imperfecta and presence of clubfoot are the other distinguishing characteristics of BS[5].

Osteogenesis imperfecta (OI) is a well-documented bone fragility disorder caused by mutations in two genes, *COL1A1* (17q21) and *COL1A2* (7q21-q22), which contribute to the formation of the type 1 procollagen[6]. Leroy et al.[7] demonstrated that there was no mutation in the *COL1A1* or *COL1A2* genes, and cultured fibroblasts did not reveal any alterations in type 1 and 3 collagens among the patients with BS. Additionally, Breslau-Siderius et al.[8] documented normal secretion of type 1 collagen without any modification in affected children from three families with BS. Bank et al.[9] showed reduced hydroxylation of lysine residues specifically derived from collagen telopeptides of bone tissue, but not in cartilage or ligamentous tissue, and suggested that the molecular defect underlying BS is a deficiency of bone-specific telopeptide lysyl hydroxylase. A genome-wide homozygosity scan in one consanguineous family identified a locus at chromosome 17 (17p22, Bruck syndrome type 1)[9]. The study of two further families did not link to chromosome 17, and had mutations in the gene *PLOD2* on chromosome 3, which codes for the putative telopeptide lysyl hydroxylase (Bruck syndrome type 2)[10]. Subsequently, Ha-Vinh et al.[2] reported a patient with BS who was presented with a novel mutation leading to an Arg598His substitution in the *PLOD2* gene. However, mutations in the *PLOD2* gene have not been demonstrated in all of the patients with BS, and further, the precise genetic locus of type I BS, which was defined in only one consanguineous family, is unclear. Recent studies have demonstrated a new gene, *FKBP10* (17q21.2), associated with autosomal-recessive OI and BS encoding FK506 binding protein 10, which is suggested to have functions in peptidyl prolyl cis-trans isomerase and chaperone capability[3]. Kelley et al.[3] speculated that *FKBP10* mutations may be the possible cause of BS type 1. Despite the molecular genetic investigations, the proportion of both types of BS is unclear, and phenotypic correlations are missing.

The common radiographic findings seen in BS are bowing of long bones with multiple fractures, generalized osteopenia and Wormian bones in the skull. Joint contractures in BS are usually bilateral and symmetrical; they are encountered in both the large and small joints. The ankle is the most common site of contracture followed by the knees and elbows, respectively. OI patients can manifest asymmetrical joint contractures after fractures, whilst the BS patients demonstrate the contractures before fractures develop[11]. The disease progresses seriously in all patients and leads to severe limb deformities, short stature, progressive kyphoscoliosis, and multiple fractures.

The contracture component of the disease results in rapid clinical deterioration, and surgical intervention does not appear to be beneficial. While meticulous orthopedic care with physiotherapy is crucial, bisphosphonates are challenging compounds for treating patients with BS.

Bisphosphonates participate in a class of drugs that are potent inhibitors of bone resorption. These compounds have been used widely to prevent the loss of bone mass in adults suffering from osteoporosis. Pamidronate is a bisphosphonate compound, and cyclical pamidronate infusions have been used in children with OI or BS safely and effectively for the last decade[12]. Side effects are rare, with an "influenza-like" reaction being the most common, which is usually encountered after the first dose of infusion[13]. The recommended administration of pamidronate is 1 hour infusion of 0.5 mg/kg/day in 100 ml saline solution for three days, repeated every two months[12]. Although there is a physiological decrease of ALP in infancy, pamidronate treatment dramatically decreases ALP levels; thus, it is postulated that ALP activity reflects the efficiency of pamidronate treatment[12].

In conclusion, this is the first association of BS with gastroschisis, and thus the case is unique. Although this association seems to be a coincidence, investigation of umbilical coelom remnants for collagen morphology and molecular genetic studies may find a relationship between these two distinct disorders. Additionally, cyclic pamidronate administration is a good choice of treatment for bone fragility in BS to reduce the number of fractures, and may be beneficial for the subsequent clinical deterioration of the patients.

REFERENCES

1. Viljoen D, Versfeld G, Beington P. Osteogenesis imperfecta with congenital joint contractures (Bruck syndrome). Clin Genet 1989; 36: 122-126.
2. Ha-Vinh R, Alanay Y, Bank RA, et al. Phenotypic and molecular characterization of Bruck syndrome (osteogenesis imperfecta with contractures of the large joints) caused by a recessive mutation in PLOD2. Am J Med Genet A 2004; 131: 115-120.
3. Kelley BP, Malfait F, Bonafe L, et al. Mutations in FKBP10 cause recessive osteogenesis imperfecta and Bruck syndrome. J Bone Miner Res 2011; 26: 666-672.
4. Klein MD. Congenital defects of the abdominal wall. In: Grosfeld JL, O'Neil JA Jr, Fonkasrud EW, Coran AG (eds). Pediatric Surgery (6th ed) Vol. 1. Philadelphia, PA: Mosby; 2006: 1157-1171.
5. McPherson E, Clemens M. Bruck syndrome (osteogenesis imperfecta with congenital joint contractures): review and report on the first North American case. Am J Med Genet 1997; 70: 28-31.
6. Mokete L, Robertson A, Viljoen D, Beighton P. Bruck syndrome: congenital joint contractures with bone fragility. J Orthop Sci 2005; 10: 641-646.
7. Leroy JG, Nuytinck L, De Paepe A, et al. Bruck syndrome: neonatal presentation and natural course in three patients. Pediatr Radiol 1998; 28: 117-119.
8. Breslau-Siderius EJ, Engelbert RH, Pals G, van der Sluijs JA. Bruck syndrome: a rare combination of bone fragility and multiple congenital joint contractures. J Pediatr Orthop B 1998; 7: 35-38.
9. Bank RA, Robins SP, Wijmenga C, et al. Detective collagen cross-linking in bone, but not in ligament or cartilage, in Bruck syndrome: indications for a bone-specific telopeptide lysyl hydroxylase on chromosome 17. Proc Natl Acad Sci USA 1999; 96: 1054-1058.
10. Van der Slot AJ, Zuurmond AM, Bardoel AF, et al. Identification of PLOD2 as telopeptide lysyl hydroxylase, an important enzyme in fibrosis. J Biol Chem 2003; 278: 40967-40972.
11. Blacksin MF, Pletcher BA, David M. Osteogenesis imperfecta with joint contractures: Bruck syndrome. Pediatr Radiol 1998; 28: 117-119.
12. Andiran N, Alikasifoğlu A, Alanay Y, Yordam N. Cyclic pamidronate treatment in Bruck syndrome: proposal of a new modality of treatment. Pediatr Int 2008; 50: 836-838.
13. Datta V, Sinha A, Saili A, Nangia S. Bruck syndrome. Indian J Pediatr 2005; 72: 441-442.