CASE REPORT

MUTATION IN FKBP10 GENE CAUSE BRUCK SYNDROME 1 (BRKS1) IN A PAKISTANI FAMILY OF PASHTUN ORIGIN

Usman Tauseef, Mohsina Ibrahim, Noshaba Noor, Misbah Hanif

National Institute of Child Health, Karachi,

Background: Bruck syndrome or BRKS1 is an extremely rare condition characterized by the onset of fractures in infancy, joint contractures, short stature, severe limb deformity, and progressive scoliosis. Less than fifty cases of BRKS1 have been reported so far. Here, we report Bruck syndrome 1 in two siblings who belong to a consanguineous Pashtun family living in Karachi. Our first case is a seven years old boy who presented with recurrent fractures, lower limb deformity, and unable to walk. He had markedly reduced bone mineral density (BMD) and a normal bone profile. The other sibling presented at one week of age with arthrogryposis multiplex congenita, post-axial polydactyly of both feet and spontaneous fracture of the right proximal femur. Genetic testing of our cases was performed in which genomic DNA was enriched for targeted regions using the hybridization-based protocol, and DNA sequencing was done using Illumina technology; both cases were found homozygous for pathogenic variant c.344G>A (p.Arg115Gln) in FKBP10 gene leading to the diagnosis of BRKS1. FKBP10 gene mutation has been reported earlier in association with BRKS1, but in our case report, we have reported the first case of BRKS1, particularly in the Pakistani population of Pashtun ethnicity. We have reported post-axial polydactyly of both feet and spina bifida for the first time in association with FKBP10 mutation. In addition, the skeletal survey of patients with BRKS 1 is elaborated in detail in this report.

Keywords: Bruck syndrome 1, FKBP10, Arthrogryposis-like disease, Pashtun, Pakistan.

Citation: Tauseef U, Ibrahim M, Noor N, Hanif M. Mutation in FKBP10 Gene Cause Bruck Syndrome 1 (BRKS1) in a Pakistani Family of Pashtun Origin. J Ayub Med Coll Abbottabad 2023;35(2):341–7.

DOI: 10.55519/JAMC-02-11056

INTRODUCTION

Bruck syndrome (BRKS) is the extremely rare autosomal recessive variant of osteogenesis imperfecta (OI). It comprises two subtypes, BRKS1 and BRKS2, which occur due to the abnormality in FKBP10 and PLOD2 genes. Both subtypes are phenotypically identical, and the hallmark of BRKS is bone fragility and severe osteopenia evidenced by the onset of bone fractures in infancy or early childhood without the history of trauma, congenital joint contractures, postnatal short stature, progressive kyphoscoliosis and severe skeletal deformities.[1,2]

The bruck syndrome was reported by German physician Alfred Bruck in 1897, who described a rare case of a patient with recurrent spontaneous fractures and peculiar deformities for the first time in Berlin. In 1964, Sharma and Anand reported a case of an Indian boy who had clinical features of OI along with Arthrogryposis multiplex congenital of knee and ankle joints with a bilateral club foot and blue sclera.[3] Petajan *et al*. (1969) described an Arthrogryposis-like syndrome having multiple joint contractures in the Eskimo inhabiting the Kuskokwim Delta which was named Kuskokwim disease. Viljoen *et al*. (1989) reported five cases from South Africa from three families who had congenital symmetrical joint contractures in the lower limb, pterygium and had fractures after minor trauma and wormian bones in the skull X-Ray and they concluded that this is the same disorder that was reported earlier by Bruck and hence recommended that the disorder be called Bruck syndrome.[4]

Brenner *et al*. (1993) described a case of a male patient with OI in Europe with recurrent fractures and congenital contractures of the elbow, knee, and ankle joints, and the patient had white sclera, short stature, and severe scoliosis. McPherson and Clemens (1997) reported a patient with rib fractures and congenital contractures associated with pterygia, club feet, torticollis, short stature, and severe kyphoscoliosis. The patient had average intelligence, normal dentine and hearing, and did not have a blue sclera.[3] In 1998, Breslau-Siderius *et al*. reported Bruck syndrome in three children of a Kurdish family with severe contractures, recurrent fractures, and kyphoscoliosis. Alanay *et al*. (2010) reported FKBP10 mutation in five Turkish families of Black Sea origin and a Mexican-American family

who had multiple deformities and were clinically diagnosed with moderately severe recessive OI.[5]

Shaheen *et al*. (2010) described a novel FKBP10 mutation in two siblings of a family belonging to Central Saudi Arabia with typical features of Bruck syndrome with a tendency to develop recurrent fractures and multiple joint contractures. In both the patients, the severity and frequency of fractures reduced after the bisphosphonate therapy.[6] Kelley *et al*. (2011) demonstrated a relation between FKBP10 mutation localized to chromosome 17q21.2 and recessive OI and BRKS1 in 5 unrelated families of South African, Turkish, Caucasian, and Indian origin respectively who shared the phenotypic features of osteopenia, recurrent fractures, congenital contractures, and severe deformity.[7] Setijowati *et al*. (2011) described 5bp deletion in FKBP10 in an Indonesian patient with BRKS1 having bone fragility and congenital joint contractures.[8]

Zhou *et al*. (2014) described mutation in FKBP10 and PLOD2 genes in two unrelated Chinese families with features of BRKS mainly recurrent fractures, arthrogryposis multiplex congenital, progressive scoliosis, and postnatal short stature. Intravenous Zoledronic acid infusion along with calcium and vitamin D supplementation was found beneficial in both cases.[9] Muhammad Umair *et al*. (2016) described FKBP10 gene mutation in three consanguineous families of Pakistani origin who were clinically diagnosed with autosomal recessive OI. All three families had multiple fractures, kyphoscoliosis, skeletal deformities, and restricted movements and members of two out of three families also had bilateral flexion contractures of the knee and elbow and bilateral extension contractures of the ankle. Screening the FKBP10 gene revealed a novel nonsense variant in one family, a missense variant in the second, and duplication of a nucleotide C generating frameshift mutation in the third family.[10,11]

In this case report, we are reporting the case of Bruck syndrome 1 in two siblings who belong to a consanguineous Pashtun family living in Karachi, Pakistan.

CASE 1

A seven-year-old boy presented with a history of being unable to walk and a deformity of both legs for two years. He had a history of falling two years back from a height of two feet, after which he developed swelling on his left hip. The patient was diagnosed with a sub-trochanteric fracture of the left proximal femur, and at that time, the hip screw fixation of the left proximal femur was done. The child partially improved in about six months but eventually ended up with a deformity of the left hip joint and got bedbound. Three months later, he developed painful swelling over the left leg, just below the knee, followed by another painful swelling of the right leg below the knee with restricted movements. At both the time, there was no history of trauma each time, and the patient managed conservatively at home, but no workup was done and both the swellings partially improved over five months. The patient also had a history of being unable to straighten his legs at his knees since birth, for which he took no other treatment apart from home remedies.

The child was born along with a twin sister to consanguineous parents via vaginal delivery, and both twins remained well after birth. The patient also has a healthy elder sister and a four months old younger brother who has also been diagnosed with Bruck syndrome 1, whose details are in the next heading. Family history is unremarkable for genetic diseases or fractures (Figure 1). Parents were also phenotypically normal. The patient had a significant delay in gross motor milestones, while adaptive, language and social milestones were achieved timely.

A general physical examination revealed a thin and lean child. The sclera was white; the teeth were mal-aligned but normal. There was no facial dysmorphism present and the vision and hearing were also normal. Weight and height were lying at a Z-score of -4.11z and -4.54z. The musculoskeletal examination of the upper limb revealed no abnormality, and the systemic examination was unremarkable.

On lower limb examination, the patient had flexion contractures of 105^{o} and 110^{o} at the right and left knee, with both legs held in a fixed flexed position at knee joints, but there was no pterygium. In addition, there was a distinctly pointed swelling at the left hip joint, 6 cm below the anterior superior iliac spine, indicating a hip screw fixator and a diffuse swelling was noted on the right shin about 8 cm below the knee joint and on the left shin about 9 cm below knee joint suggestive of a partially healed fracture of both tibiae. The range of movements was restricted and painful at the left hip and both legs. No deformity or anomaly was present in the upper limb, spine, chest, and normal male genitalia (Figure 2).

In the lab results, the patient had normal values of serum Ca^{+2} (9.6mg/dl), Mg^{+2} (2.3 mg/dl), $PO4^{-2}$ (5.6 mg/dl), 25-hydroxy vitamin D

(34 ng/ml-sufficient) and intact PTH (31 pg/ml) and mildly elevated Alkaline phosphatase (412 U/L). Serum electrolytes and a complete blood count were also within normal limits.

A skeletal survey revealed generalized diffused osteopenia with cortical thinning and prominent trabeculations with remodelling changes due to softening of bones. The bone age was 4.5 years calculated by Greulich and Pyle's method (reduced in comparison to the chronological age of seven years). In the skull, multiple wormian bones were noted in the line of sutures. The ribs were gracile and tubulated, and old fractures were identified at the eight ribs on the left side and the ninth rib on the right side. Spina bifida at the lower lumber and upper sacral region was also noted. In the upper extremity, a partly healed spiral fracture of the proximal shaft of the left humerus was identified, along with growth arrest lines in the distal radius and proximal ulna. The lower extremity has an abnormal configuration of the right hemipelvis with remodelling changes.

The left femur and both tibiae were significantly bowed, protusio-acetabuli was noted on the right side and limb length discrepancy was seen. Pronounced bilateral coxa vara identified with angulation $<120^{o}$ more towards left with lateral bowing of the proximal femur representing shepherd crook deformity. Healing fractures at the upper-mid shaft of both tibia bones were seen, and a complete partially healing fracture with callus formation was identified at the proximal shaft of the left femur with periosteal reaction and evidence of inter-fixation with pinning seen just above the fracture (Figure 3).

Bone Mineral Density (BMD) DEXA Scan was carried out, suggesting a markedly reduced cumulative BMD over the left hip and lumbar spine with a Z score of -5.6 SD over the left hip (BMD: 0.184 gm/cm^2), -7.3 SD over the left femoral neck (BMD: 0.153 gm/cm^2) and -3.3 SD over the spine (BMD: 0.369 gm/cm^2).

The intravenous Pamidronate therapy was started along with oral calcium and vitamin D supplementation, and the patient is on regular follow-up. The patient is currently wheelchair dependent and unable to carry out activities of daily living without assistance.

CASE 2

Our second case is the younger brother of case 1, who is currently four months old. The child presented in the first week of life with a complaint of swelling over the right thigh for two days. The child was born via vaginal delivery at home, assisted by a midwife.

On examination, the patient had no facial dysmorphism. The sclera was white. On musculoskeletal examination, the patient had fixed flexion contractures of the elbow, wrists, and knee joints bilaterally with pterygium. He had bilateral club feet with post-axial polydactyly of both feet. Systemic examination, genitalia, and back examination were unremarkable (Figure 4).

An initial X-Ray showed a fracture at the upper third of the shaft of the right femur. The patient was managed conservatively, and the genetics was sent and followed.

In the Skeletal survey, there was generalized reduced bone density, and multiple wormian bones were noted across suture lines of the skull. There were multilevel old healed fractures with callus formation involving multiple ribs bilaterally. Multiple fractures of variable ages were present in the femur, proximal tibia and proximal humerus, distal radii, and ulna with bowing deformity. Fixed flexion contractures were noted at both elbow and knee joints. Bilateral club feet were also noted with post-axial polydactyly on both feet (Figure-5). The patient is four months old and he is currently having a fifth-time fracture mainly involving long bones of the lower limb which is managed conservatively by the orthopaedic team.

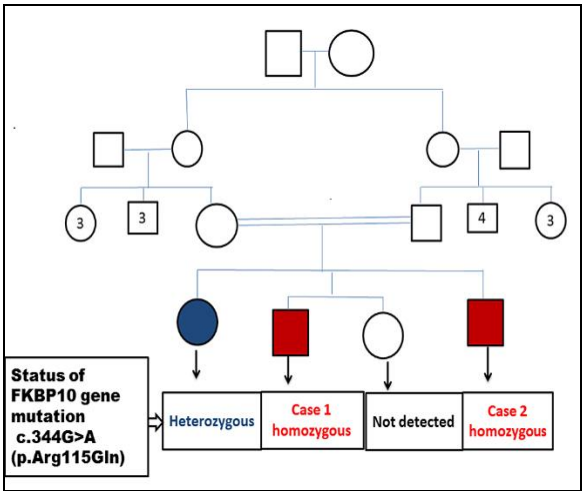

Figure-1: Family pedigree of both cases. Both male siblings with the phenotypic of Bruck syndrome were found homozygous for the FKBP10 gene mutation. The elder sister was heterozygous for the same genetic mutation, but in the twin sister of case 1, the mutation was not detected. Parents were also phenotypically normal.

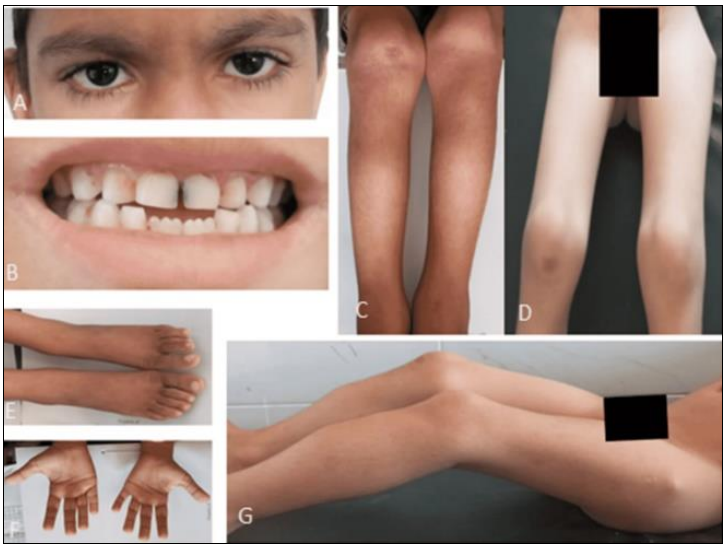

Figure 2: Clinical phenotypes of case 1.

(A) Normal white sclera is appreciable, (B) No dentinogenesis imperfecta, (C) Swelling noted bilaterally on upper shins which were tender at the time of examination, representing partially healed fractures of both tibia, (D) prominent projection of hip screw fixator noted on the left lateral aspect of the hip, (E and F) Normal hand and feet (no polydactyly), (G) Fixed flexion contracture of 105^{o} and 110^{o} at right and left knee due to which both legs are held in a fixed flexed position, no pterygium at the knee joint.

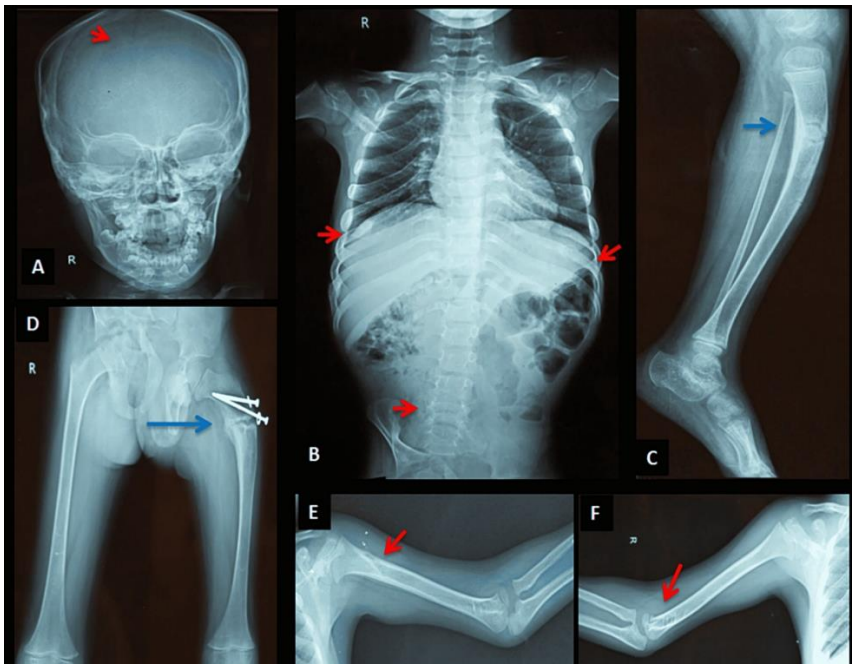

Figure 3: Skeletal survey findings of case 1

Marked generalized osteopenia with cortical thinning and prominent trabeculations are noted. (A) Multiple wormian bones in the line of sutures (red arrowhead). (B) Ribs appear tubulated and gracile, with old fractures identified on the left 8th rib posteriorly and at the angle of the left 9th rib. Spina bifida is identified at the lower lumber and upper sacral region (small red arrows). (C) Multiple healing fractures at the upper mid-shaft of the tibia with obvious bowing (small blue arrow). (D) Abnormal configuration of right Hemi pelvis with remodeling changes due to softening of bones, protusio-acetabuli on right side resulting in limb length discrepancy. Bilateral pronounced coxa vara angulation < 120^{o} but more on the left and lateral bowing of proximal femur representing shepherd crook deformity. A complete partially healing fracture with callus formation is identified at the proximal shaft of the left femur with inter-fixation with pinning seen just above the fractures (long blue arrow). (E and F) Partially healed spiral fracture of the proximal shaft of left humerus and growth arrest lines noted at distal humeri and proximal right ulna (large red arrows).

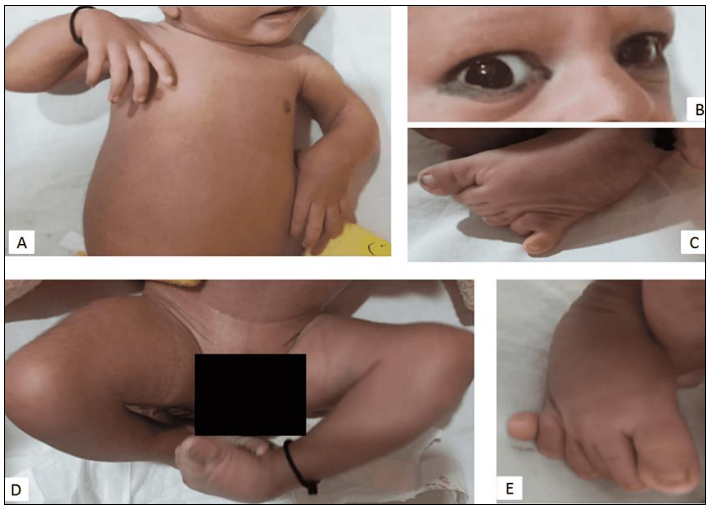

Figure 4: Clinical phenotypes of case 2.

Fixed flexion contractures were seen at both elbows with pterygium (A). A normal white sclera (B). Fixed flexion contractures of both knees with pterygium, bilateral club foot, and swelling over the right proximal thigh, representing healing fracture of shaft of the right femur (D). Post-axial polydactyly of both feet (C and E).

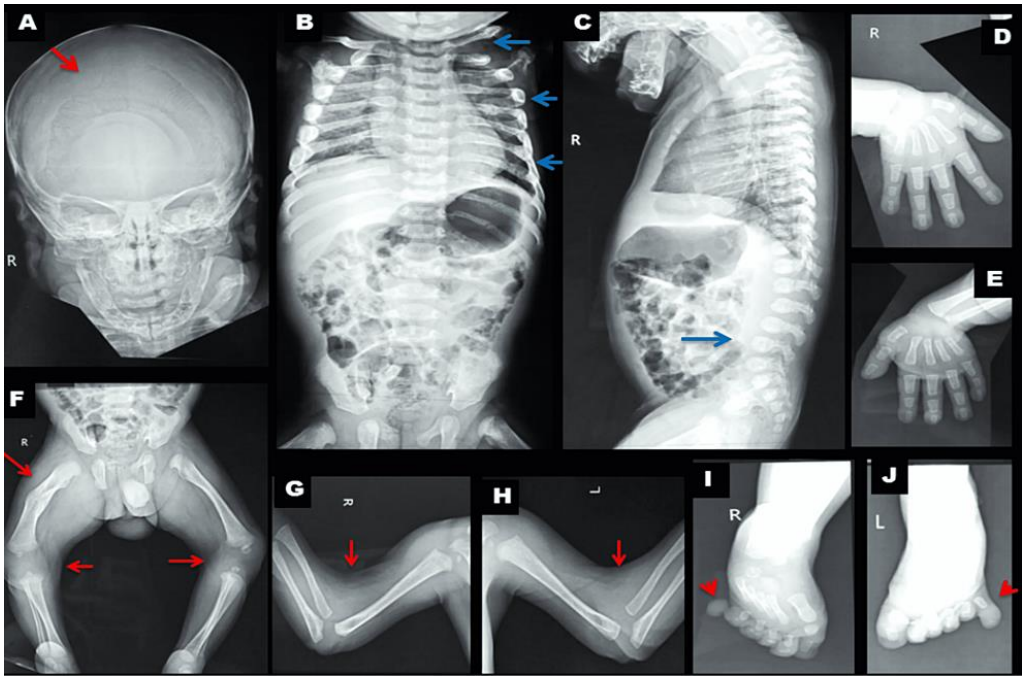

Figure 5: Skeletal survey findings of case 2.

Marked generalized osteopenia was noted with cortical thinning and prominent trabeculations. (A) Multiple wormian bones in the line of sutures (red arrows). (B and C) Significantly deformed ribs with bowing deformity. Multilevel old healed fractures with callus formation on the right side, involving 1 to 6th ribs. A healed fracture at the lateral end of the left clavicle, along with complete un-displaced fracture lines involving the 9th, 10th, and 11th rib on the left side (small blue arrows). Reduced height of multilevel dorso-lumbar spine with aberrant widened intervertebral disc spaces noted suggestive of platyspondyly (large blue arrow). (D and E) Bone age is one month, and no polydactyly in hand digits. (F) Complete displaced fracture of the right pubic ramus. An old healed fracture at the mid-shaft of the right femur with exaggerated callus formation and linear periosteal reaction. Multiple fractures of variable ages with callus formation and periosteal reaction were noted at both femur and proximal tibia. (G and H) Fixed flexion contractures are seen on the anterior aspect at elbow joints bilaterally, along with pterygium (small red arrows). Multiple fractures of variable ages with callus formation and periosteal reaction at both humeri proximally, left distal radius and both distal ulna. (I and J) Bilateral club feet noted with an extra digit towards the little toe representing post-axial polydactyly. Soft tissue nubbin is present on the right side without a definite extra digits (red arrowheads).

RESULTS

Diagnostic gene testing (for osteogenesis imperfecta and bone fragility panel) was performed in which sequential analysis and deletion/duplication testing of the 46 genes was evaluated that are associated with bone fragility.

The genomic sample of patients was enriched for targeted regions using a hybridization-based protocol and sequenced using Illumina technology. All targeted regions were sequenced with ≥50x depth or were supplemented with additional analysis.

As a result, two Pathogenic variants were identified in theFKBP10 gene, and both patients were found homozygous. In our cases, two pathogenic variants, c.344G>A (p.Arg115Gln) (homozygous), were identified in FKBP10, Exon 2. This sequence replaces arginine with glutamine at codon 115 of the FKBP10 protein (p.Arg115Gln). The FKBP10 gene is associated with Bruck syndrome (MedGen UID: 342431) and autosomal recessive osteogenesis imperfecta (MedGen UID: 462568).

The elder sister was identified heterozygous for a pathogenic variant, c.344G>A (p.Arg115Gln) in the FKBP10 gene, and a carrier for FKBP10-related conditions, while no reportable genetic variants were identified in the twin sister of case 1.

DISCUSSION

Bruck syndrome (BRKS), also known as Kuskokwim disease or Arthrogryposis-like disorder, is an autosomal recessive condition comprising bone fragility, early-onset bone fractures, congenital joint contractures, and progressive skeletal deformities.[3] It has been classified into two types according to the genotype. The loss of function mutations of the FKBP10 gene on chromosome 17q21.2 results in Bruck syndrome 1; BRKS1 (MIM 607063), while a homozygous mutation in the PLOD2 gene on chromosome 3q24 results in Bruck syndrome type 2; BRKS2 (MIM 601865).[2] Less than fifty patients with this syndrome have been reported so far.[12,13]

FKBP10 (FKBP10 Prolyl Isomerase 10 or FK506-Binding Protein10) gene encodes the FKBP65 protein (65-kDa FK506-binding protein) which is a member of a highly conserved family of intracellular receptors, also called immunophilins that are responsible for carrying peptidyl-prolyl-isomerase (PPIase) activity.[1] These immunophilins localizes in the endoplasmic reticulum catalyze the cis-trans isomerization of peptide-Prolyl bonds and are involved in folding and trafficking events. The expression of FKBP10 is limited to bone, tendons, and ligaments where they are believed to assist in collagen folding.[10,14] Diseases associated with FKBP10 gene mutation are Bruck syndrome 1 (BRKS1) and Osteogenesis imperfecta type XI (OI XI) respectively, both of which are characterized by bone fragility, fractures and/or joint contracture.[15]

The clinical presentation of BRKS 1 is highly variable and ranges from mild to severe lethal disease. The phenotypic variability of cases with BRKS1 ranges from only fractures without contractures, only contractures, or with both fractures and contractures.[1] The age of onset of fractures also vary, some patients start developing fractures in utero while other had no fracture till the first decade of life, and the number of fractures also differ from patient to patient as in one previous case report of a six-year old male had 45 fractures with debilitating flexion contractures while his five-year old sister had 15 fractures with minimal flexion contractures.[16,17]

Clinical features of BRKS and OI overlap with each other. Typical features of BRKS1 include lower limb and rib fractures occurring with minimal or trivial trauma leading to debilitating deformities, flexion contractures, pterygium at the elbows and knees, torticollis, and club feet. Patients possess normal intelligence, but severe kyphoscoliosis and short stature might affect their pulmonary function.[3,18]

The most common sites of fractures in BRKS1 are diaphysis of long bones, especially femur and tibia, but fractures can occur in long bones of the upper limb as well as in vertebra, clavicle, ribs, and pelvis, and common sites of contractures are large joints such as the knee, elbow, ankle and wrist.[3,16] The characteristic clinical features of OI such as blue sclera, hearing loss, and dentine abnormality may not be present in BRKS1.[16]

Radiologic features of Bruck syndrome include bone demineralization fractures, deformity, wormian bones in the skull, vertebral wedging, and cystic changes at old fracture sites.[3,16]

Intravenous bisphosphonate therapy is the currently used standard medical treatment for patients with FKBP10 variants (OI XI and BRKS1). Pamidronate is the most commonly used drug in this category, and it is administered in divided doses for three days at two to four months intervals, whereas zoledronic acid is given biannually as a single dose.

Bisphosphonate therapy has shown encouraging results in OI XI in terms of annual improvement of bone mineral density (BMD) and decreasing the number of annual fractures in patients with BRKS1.[9] But on the contrary, no significant response has been noted in terms of decreasing the rate of scoliosis progression and long bone deformity and unfortunately bisphosphonate treatment has also not proved helpful in preventing disability in patients with OI XI and BRKS1 and most of the patients who received this therapy when followed were unable to walk and were wheelchair dependent.[16,19] Treatment options for the management of contracture and deformity include serial casting and soft-tissue release. Physical therapy and bracing have also been proven to help delay the progression of contractures. To retain the movement of joints, soft tissue surgeries can be performed. Intramedullary nail fixation in angulated

fractures and casting in fractures without deformity had successful results. Spinal fusion can be used for deformities related to the spine.[16] Experts suggest follow-up monitoring of bone density with DEXA scans, calcium, and vitamin D supplements along with bisphosphonates for improvement. Thus periodic evaluation, long-term pain management, and management of disability are necessary to improve the quality of life in patients with BRKS1.[20]

The phenotypic presentation of OI and BRKS1 are similar, so genetic testing plays an essential role in making the diagnosis and research is going on to utilize whole exome sequencing for prenatal diagnosis.[2,17]

CONCLUSION

In conclusion, we have reported the first case of Bruck Syndrome 1 in the Pakistani population having FKBP10 gene mutation. We have also reported polydactyly and spina bifida in association with Bruck syndrome 1, that has not reported earlier. Moreover, we have gone through the clinical and radiographic features of the disease in detail, and we hope that our study will help to enhance our understanding of the clinical phenotypes of this disease. Further research is needed to find methods that improve the quality of life.

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Submitted: June 07, 2022	*Revised: September 21, 2022*	*Accepted: October 10, 2022*

Address for Correspondence:

Dr. Usman Tauseef, National Institute of Child Health, Karachi-Pakistan
Cell: +92 323 8229360
Email: usman.tauseef.dr@gmail.com