Case Report

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Bruck Syndrome (Bone Fragility with Congenital Joint Contractures): A Case Report

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Abstract

Background: Bruck syndrome is a disorder in which features of osteogenesis imperfecta and arthrogryposis multiplex congenita coexist. It is an extremely rare condition with less than 40 cases reported worldwide.

Case presentation: We describe the case of a girl child, born of a consanguineous marriage, who, at birth, was noted to have flexion contractures of both knees and elbows as well as right clubfoot. Post-natally, she developed repetitive fractures of both femurs occurring with trivial trauma. She presented to us at the age 8.5 years, with short stature and inability to stand due to the severe knee flexion contractures. She also had flexion contractures at bilateral elbows. Intelligence and fine motor skills were normal. Sclerae, teeth and hearing were also normal. Radiographs revealed osteoporosis, severely deformed femora and vertebral body flattening. A diagnosis of Bruck syndrome was made on the basis of clinical findings. Genetic testing was offered, but declined by the child's parents. She has since undergone osteotomies and rodding for both femurs, and bilateral distal femoral anterior hemi-epiphysiodesis for gradual correction of knee contractures. She is on cyclical pamidronate therapy to address bone0 fragility.

Conclusion: In this report, we describe the diagnostic features and management of this rare syndrome, and provide a summary of the existing literature on the disorder.

Keywords: Bruck syndrome,Osteogenesis imperfecta, Arthrogryposis, Congenital joint contractures, Bone fragility

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DOI- 10.13107/ijpo.2021.v07i03.120 | www.ijpoonline.com

Introduction

Bruck syndrome (BS) is an extremely rare condition in which congenital joint contractures are associated with bone fragility. Less than 40 cases of this syndrome have been reported worldwide [1], including two from India [2, 3]. We report a case of this rare disorder and provide a synopsis of its orthopaedic manifestations and management. In resource-poor settings, confirmation of such rare diseases by genetic analysis is not always possible; knowledge of the syndromic association between joint contractures and skeletal fragility is essential for accurate diagnosis and appropriate treatment.

The aim of this report is to make readers aware of this rare syndrome, and to highlight the need to look for features of osteogenesis imperfecta when assessing an infant born with multiple joint contractures.

Case Presentation

A 2.75 kg baby girl was born at 38 weeks gestation by spontaneous vaginal

Submitted: 7 July 2020; Reviewed: 20 September 2020; Accepted: 13 October 2020; Published: 10 May 2021

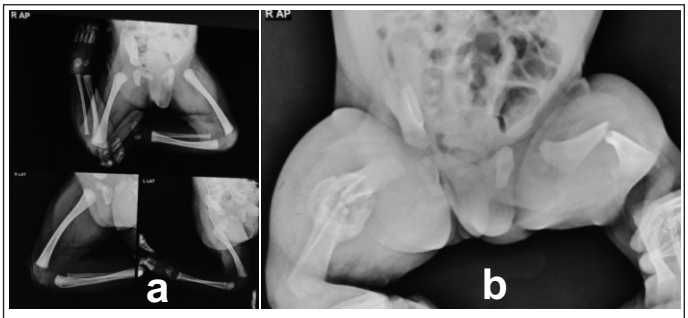

Figure 1: Plain radiographs of both lower limbs soon after birth.
a: Anteroposterior (AP) and lateral view radiographs at day two of life. Note the severe flexion contractures at both knees. The hips are contained and bone quality appears to be normal.
b: Lateral view radiograph of both femurs at 21 days of life. Note the fresh fracture of the left femur shaft, and the old right femur fracture that is healing with abundant callus

delivery. She was the first issue, born of a consanguineous marriage between first cousins. The antenatal period had been uneventful and an anomaly scan at 22 weeks had been reported as normal. The mother's first conception ended in a first-trimester miscarriage. The parents' second issue, born six years later, was a healthy boy.

Immediately after birth, the baby was noted to have flexion contractures at both knees and elbows (Fig. 1a), as well as right sided clubfoot. The first fracture occurred at day five of life; the right femur shaft fractured within hours of applying a brace that attempted to correct the knee flexion deformity. Subsequently, the left femur fractured on day 21 (Fig. 1b). Both fractures healed with conservative management. Over the next eight years, the child sustained approximately 20 femoral shaft fractures, 12 on the left and eight on the right. The fractures united uneventfully, and the child was reported to be active and playful in between fractures. No bones other than the femurs sustained fractures.

Soon after birth, manipulation and stretching were performed diligently by the mother. Braces for the lower limbs were discontinued due to repeated fractures. Elbow extension splints were used for several years and improvement were noted in the upper limb contractures. At the age of three years, the right clubfoot was treated with Tendoachilles lengthening and posterior soft tissue release. Thereafter, serial castings were performed in an attempt to stretch out the knees. Although significant improvement in knee extension was obtained, the contractures recurred soon after casting was discontinued, despite the use of braces.

At presentation to our institution, the child was 8.5 years old and weighed 14 kg (below the 3rd percentile for age). She had short stature – length was 106 cm when measured with the tape placed along the flexed limbs and 98 cm when measured from head to heel (below the 3rd percentile for age). She had severe

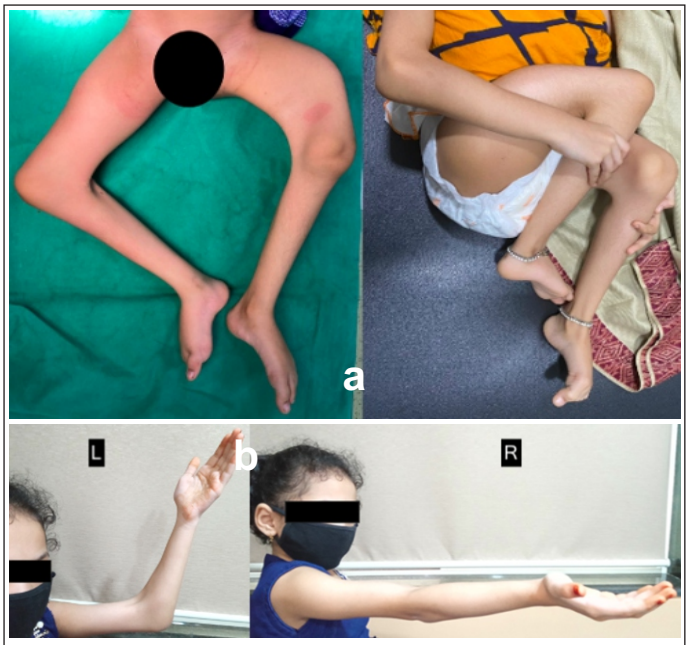

Figure 2: Clinical pictures at presentation demonstrating the flexion contractures.
a: Bilateral knee flexion deformities. Note the severe bowing of the left femur.
b: Flexion deformities at both elbows, left worse than right

flexion contractures at both knees (90° and 70° on the right and left respectively), and both elbows (20° and 80° on the right and left respectively); with further full flexion possible (Fig. 2 a and b). In contrast, the small joints of the hands and feet were hyper-lax, as evidenced by >90° passive dorsiflexion at the little fingers and ability to passively dorsiflex thumbs up to the flexor aspects of the forearms. Both feet were plantigrade. She had white sclerae, normal teeth, normal hearing and no dysmorphic facial features. The spine and chest were normal.

Her cognitive function was normal. Power in both upper and lower limbs was 3+. All milestones had been attained normally, within the limits of her deformities. Range of motion at both hips was full, and she was able to sit upright without support. Although she was unable to stand due to the severe knee flexion, she was able to ambulate with a bicycle. There was no family history of either joint contractures or bone fragility.

Old radiographs demonstrated multiple fractures over the previous 8 years. All had healed with adequate callus. Skull X-ray was normal with no Wormian bones. Both femurs were severely bowed, whereas the tibiae were relatively straight (Fig. 3 a and b). All bones were osteopaenic (Fig. 3c). Serum calcium was 10.1 mg/dL, phosphorus 4.6 mg/dL, alkaline phosphatase 232 U/L and 25-hydroxy Vitamin D 20.68 ng/mL. The family was recommended to have genetic analysis but declined due to financial constraints.

The child's parents were counselled about the nature of the disorder and its prognosis. Goal of treatment was correction of the lower limb deformities so as to allow ambulation.

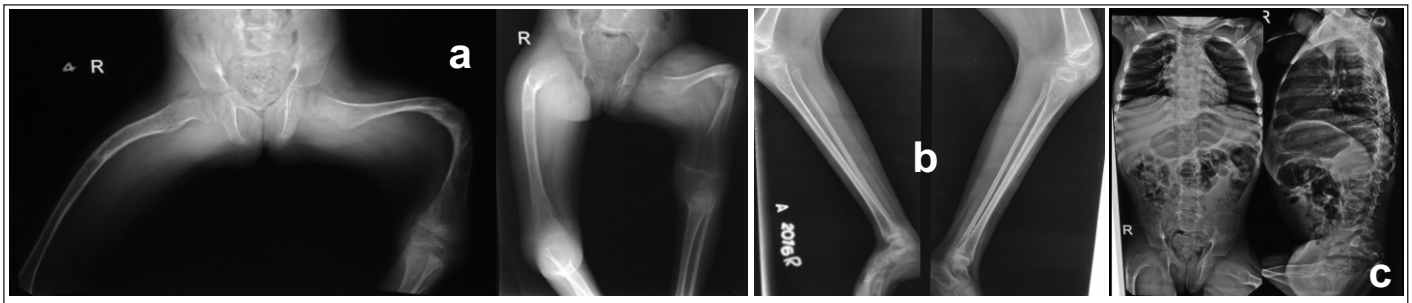

Figure 3: Radiographs at presentation, aged 8.5 years.
a: AP and lateral view radiographs of bilateral femora. Note the osteopaenia and signs of healed fractures. There is >90° angulation of the left femoral shaft on both views.
b: Lateral view radiographs of bilateral tibiae showing gracile bones (narrowed at the shafts) but no angulation.
c: AP and lateral views of the spine showing platyspondyly of multiple vertebral bodies with increased disc spaces

Corrective osteotomies and rodding were performed sequentially for both femurs. Partial correction of knee flexion deformity was achieved by performing femoral shortening at the time of corrective osteotomy. Simultaneously, anterior eight plates were inserted at bilateral distal femurs so as to allow gradual correction of the residual flexion deformities. Clinical pictures and radiographs after surgery are given in Fig. 4 a-c. In consultation with a paediatric endocrinologist, the patient was started on intravenous Pamidronate therapy (1 mg/kg, every two monthly). We plan to begin assisted mobilization once sufficient knee extension has been obtained.

Discussion

Iin 1989, Viljoen et al described five children with symmetrical contractures of the knees, ankles and feet, associated with frequent fracturing [4]. They postulated a syndromic identity for this disorder and suggested the eponym 'Bruck syndrome' to describe it, in view of a similar case being documented by Alfred Bruck in 1897 [4]. Subsequent authors noted that the patient described by Bruck had osteogenesis imperfecta (OI) and developed contractures only later in life [5]. Hence, the designation 'Bruck syndrome' is actually a misnomer but continues to be used to describe this condition.

Genetic and Molecular Basis

According to the specific gene involved, two variants of BS have been defined [6]. The defect in Type 1 BS has been traced to the FKBP10 gene, located on chromosome 17q21 [7]. It encodes a protein FKBP65 which functions as an endoplasmic reticulum collagen chaperone. Type 2 BS is caused by mutations in the PLOD2 gene, located on chromosome 3q24, which codes for a bone-specific telopeptide lysyl hydroxylase [6,8].

Mutations in either of these genes cause defects in the post-translational modification of collagen, leading to abnormal collagen folding and cross-linking, producing the bone fragility

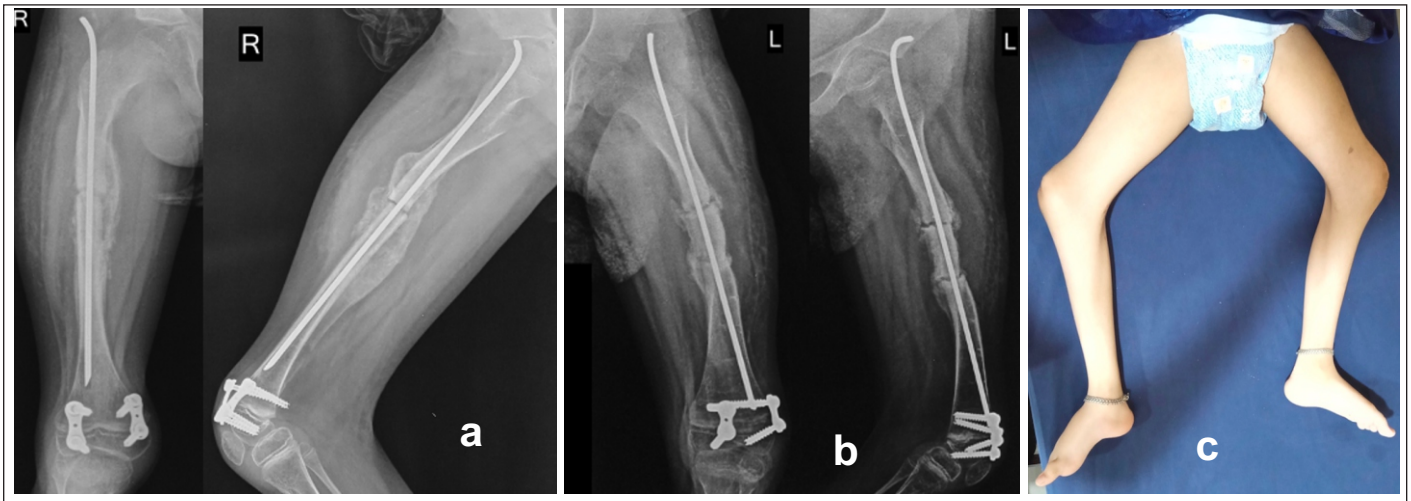

Figure 4: Clinical pictures and radiographs after surgery.
a: AP and lateral view radiographs of the right femur, four weeks after corrective osteotomy, rodding and distal femur anterior eight-plate application.
b: Radiographs of the left femur, five weeks after same procedure performed on the left.
c: Clinical photograph two months after the second surgery. The knee flexion deformity has reduced to about 50° on both sides. Further correction is expected to occur with growth

Table 1. Clinical features of Bruck syndrome [10, 11]

Height	Post-natal short stature
Ears	Normal hearing
Eyes	Blue/white sclerae
Teeth	Normal teeth
Skull	Wormian bones
Face	Dysmorphic features – Triangular face, brachycephaly
Chest	Pectus carinatum
Bones	Osteoporosis/Osteopaenia
	Bone fragility
	Bowing of long bones
Joints	Large joint contractures (Knee, elbow, hip, ankle)
	Small joint hyperlaxity (Wrist, fingers)
Spine	Kyphosis
	Scoliosis
	Vertebral body wedging/flattening
Pelvis	Acetabular protrusion
	Coxa vara
Feet	Talipes equinovarus
Skin/soft tissues	Pterygia (knees, elbow)
Intelligence / Cognitive function	Normal
Genito-urinary	Inguinal hernia*

* Reported only in BS Type 2 [5]

characteristic of BS. The pathogenesis of joint contractures in BS is not known; it is postulated to be either a primary morphogenetic defect or possibly a consequence of restriction of joint movements in utero [5].

Although tremendous progress has been made in recent years in mapping out the mutations that produce Bruck syndrome, genetic testing remains prohibitively expensive and is not accessible for many children with such rare disorders, such as the child we have reported. However, knowledge of the phenotype of this syndrome can allow diagnosis with reasonable confidence.

Inheritance

Both types of BS show an autosomal recessive mode of inheritance. The parents of an affected child have a one in four risk of passing on the condition to any further offspring [9].

Clinical Features [10, 11]

A neonate with this disorder is usually initially diagnosed as arthrogryposis multiplex congenita, and it is not until multiple fractures occur during infancy or early childhood that the syndrome is suspected [9]. The clinical findings of BS are enumerated in Table 1.

The clinical features of BS produced by FKBP10 and PLOD2 mutations are essentially the same [6]. However, variability exists among BS cases with respect to the severity of contractures and the age at onset and frequency of fractures [12]. It has recently been shown that both FKBP10 and PLOD2 mutations can produce a broad variety of phenotypes, including isolated OI (ranging from mild to severe forms) without joint contractures [13]. Such variability may even be present within the same family, with some members having OI and other members of the same family having BS [7, 12, 13].

Table 2. Differential diagnoses of osteoporosis with fragility fractures in children [14]

Primary conditions	**Genetic disorders** **•Osteogenesis imperfecta** **•Ehlers-Danlos syndrome** **•Marfan syndrome** **•Homocystinuria** **•Hypophosphatasia** **•Polyostotic fibrous dysplasia** **•Rickets (genetic forms)** **Idiopathic juvenile osteoporosis**
Secondary conditions	**Chronic inflammatory conditions** **•Systemic lupus erythematosus** **•Inflammatory bowel disease** **•Nephrotic syndrome** **Infiltrative conditions** **•Leukemia** **•Thalassemia** **Endocrine disorders** **•Hypogonadism** **•Growth hormone deficiency** **•Cushing syndrome** **•Hyperthyroidism** **Nutritional/malabsorptive** **•Vitamin D deficiency** **•Celiac disease** **•Biliary atresia** **Renal** **•Chronic renal disease** **•Secondary hyperparathyroidism** **Reduced mobility** **•Cerebral palsy** **•Muscular dystrophy** **•Post-traumatic** **Iatrogenic** **•Glucocorticoids** **•Anticonvulsants** **•Methotrexate** **•Radiation therapy**

Differential Diagnosis [14]

A number of conditions are associated with osteoporosis and increased risk of fragility fractures in childhood (Table 2). The work-up of such cases begins with assessment of bone mineral

density (BMD), for which dual-energy X-ray absorptiometry (DEXA) scanning is the preferred method. It is important to calculate Z-scores by comparison with age-, sex- and ethnicity-matched controls, as calculation of T-scores (by comparison with young adults at peak bone mass) can lead to overdiagnosis of low BMD in children.

Further testing to identify the underlying cause must be based upon the history and examination findings. Full blood counts, renal & hepatic function tests, erythrocyte sedimentation rate (ESR), serum calcium, phosphorus & alkaline phosphatase, serum 25-hydroxy Vitamin D & parathyroid hormone (PTH) levels are the preliminary investigations performed in most cases. Screening for celiac disease, bone marrow biopsy and liver biopsy may be indicated in certain cases. Genetic testing for COL1A1/COL1A2 are required in children with a clinical picture and/or family history suggestive of OI. Measurement of bone turnover markers, namely bone-specific alkaline phosphatase, osteocalcin and collagen cross-linked N-telopetide can help guide treatment. Finally, when the diagnosis remains elusive, bi-cortical iliac bone biopsy for analysis of microarchitecture, density and turnover may be necessary.

The classical clinical picture of bone fragility combined with joint contractures must give rise to a high index of suspicion for BS, however, definitive diagnosis and classification relies on genetic testing.

Treatment

Treatment of BS must include both medical measures to address the bone fragility on the one hand, and steps to correct joint contractures on the other.

In general, medical management for bone fragility requires treatment of the underlying cause wherever possible and use of bone-sparing therapies [14]. Ensuring adequate intake of calcium and Vitamin D is beneficial in all patients. Encouragement of weight-bearing activity has been shown to increase bone mass. Avoidance of contact sports and jarring activities must be emphasized. In terms of bone-sparing therapies, bisphosphonates have been proven to improve BMD, increase function and reduce pain in children with OI. The goals of treatment of joint contractures are to optimize lower limb alignment and stability for ambulation, and upper extremity mobility for self-care [15]. Soft-tissue releases should preferably be done at a younger age, before adaptive intra-articular changes occur; whereas realignment osteotomies are performed closer to skeletal maturity, to avoid recurrence. Physiotherapy and long-term bracing also play an important role in management of joint contractures.

For children with BS, non-operative treatment consists of cyclical bisphosphonate infusions and vitamin supplementation, similar to treatment of OI [12]. Trials of Pamidronate therapy in children with BS have shown results comparable to those seen in children with OI, with reduction in rate of fractures, decreased pain and improvement of clinical severity scores [16]. Joint contractures in BS are non-responsive to casting, in fact, vigorous attempts at manipulation have been shown to produce plastic deformations [9]. Use of soft tissue releases and tenotomies has been described [10, 17], however we have not come across any report of the efficacy of growth modulation in correcting contractures in BS. Fractures can usually be managed conservatively; corrective osteotomies and rodding should be performed in severely deformed bones [10, 17]. Kyphoscoliosis can be quite severe in these children, and usually progresses rapidly during adolescence; spinal instrumentation and fusion may be indicated [17].

Prognosis

Children with BS tend to have a worse prognosis than those with OI because the joint contractures interfere considerably with functionality [12]. The combination of non-ambulation and joint contractures also predisposes them to a higher rate of fractures, analogous to children with cerebral palsy.

Conclusion

With an increasing number of cases of this rare disorder being reported, it is important for orthopaedic surgeons to be aware of the clinical aspects of BS, and to be able to differentiate it from the more common forms of osteogenesis imperfecta.

Clinical Relevance

The syndromic association between congenital joint contractures and skeletal fragility is known as Bruck syndrome. Although it is the gold standard, genetic analysis for the diagnosis of such rare syndromes is not always possible in resource-poor settings. Treating clinicians must be aware of the clinical aspects of this disorder and assess for signs of bone fragility in an infant born with multiple joint contractures.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil; **Source of support:** None

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How to Cite this Article

Pinto AD, Vaidya SV | Bruck Syndrome (Bone Fragility with Congenital Joint Contractures): A Case Report. | September-December 2021; 7(3): 29-34.