Fibrodysplasia Ossificans Progressiva with Rare Familial Inheritance Pattern: A Case Series

Chandramohan Ravichandran¹, Saranya Nagalingam², Mahendra Bhat Gururaj³
¹Assistant Professor, Department of Orthopaedics, ACS Medical College and Hospital, Chennai, Tamil Nadu, India, ²Compulsory Rotatory Resident Internship, ACS Medical College and Hospital, Chennai, Tamil Nadu, India, ³Orthopaedic Consultant, Hinduja Hospital, Mumbai, Maharashtra, India

Fibrodysplasia ossificans progressive (FOP) also termed as “stone man syndrome” is an autosomal dominant disorder manifested in the form of congenital malformation of the great toes with progressive ossification of the skeletal muscle and soft tissues in a specific pattern. It is a rare disorder, usually as sporadic and isolated and very few cases have been reported. Often FOP is missed or diagnosed very late, both of which leads to rapid progression and reduced life expectancy. We report first of such a case series in India with the hereditary transmission in a family, affecting three persons. Our index case was the first daughter 17 years female who presented with stiff joints, worsening over time and her father 45 years male was also affected with his major joints fused in different positions, and her younger sister 13 years female was in the early stage of disease. Further investigations such as serum calcium, phosphorous, X-ray, computed tomography, and bone scan confirmed it as cases of FOP. We present our detailed study of the interventions, their effectiveness, the role of drugs given to reduce symptoms in FOP, and this would aid the physicians and healthcare workers to suspect/diagnose the disease.

Key words: Brachydactyly, Chin to chest deformity, Clinodactyly, Genetic disease, Hallux valgus, Microdactyly, Paraspinal nodules, Stone man syndrome

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder (some literatures terming it as a rare variant of myositis ossificans with a genetic etiology) characterized by congenital malformation of the great toes, with sometimes associated with finger deformities and by heterotopic ossification of skeletal muscle and soft connective tissue in specific anatomic patterns which is progressive.¹ It tends to affect the patients during the first decade of life with the development of inflammatory fibroproliferative masses in skeletal muscles and aponeuroses, usually in the axial region. It is progressive and ultimately forms mature heterotopic bone through an endochondral ossification.² The molecular defect causing the disorder is a heterozygous recurrent mutation, c.617 guanine> adenine, causing an R206H substitution in the ACVR1/Alkaline phosphatase (ACVR1/ALK2) gene on chromosome 2q 23-24 region that encodes for a Type I receptor for bone morphogenetic proteins.³ FOP occurs sporadically, and a lot of large studies have not provided any conclusive evidence of familial transmission.⁴ In the current report, we describe findings of FOP in a father with concomitant involvement of the same pathology in two of his children who are females.

CASE REPORTS

Case 1

A 17-year-old, first-born female child to the parents of non-consanguineous marriage, with normal birth history, and no known genetic diseases in the family and any other medical diseases was referred to us in a non-ambulatory state due to severe pain, stiffness, and multiple nodules over the back which had developed over a period of 1-year and had been progressing in size ever since (Figure 1). The patient had severe difficulty in walking with a deformity over the right hip which had developed since a month prior to referral. The patient also had difficulty in using her left arm for daily activities since a month. The patient had deformities of both the great toes in the form of bilateral hallux valgus and short toes (brachydactyly) and clinodactyly of both hands since birth (Figure 3). On examination, multiple firm nodules and swellings were noted in the paraspinal region extending along the entire spinal area and adherent to underlying soft tissues. A solitary nodule was noted over the left supraclavicular region and over the left axillary region. A fixed flexion deformity of the left hip of 40° was
noted and was revealed as there was a complete loss of lumbar lordosis and generalized flattening of the spine. The range of motion of right hip and knee are painful and shows variable resistance to passive movements. The patient was investigated in the form of routine blood investigations and serum calcium, serum phosphorus and ALP which showed values of 7.65 mg/dl (N: 9-11 mg/dl), 3.89 mg/dl (N: 2.5-5 mg/dl) and 566.80 IU/l (N: up to 130 IU/l), respectively. Serum CPK total and CPK - MM fraction were 65.10 IU/l (N: 25-170 IU/l) and 10.40 IU/l (N: up to 24 IU/l) respectively.


Case 2
On enquiring about her family, her father (45/M) gives a similar presentation over the past 13 years which as per his history started with a fall following which he started developing stiffness of his back and has been gradually progressive and now has restricted his daily activities to a great extent. On examination, the patient has a stooped posture with generalized paraspinal calcification extending over the entire spinal area (Figure 5). The patient has bilateral fixed flexion deformity of both hips of 60° with both the knees flexed to place his feet on the couch. He also has calcification over his adductor muscles bilaterally (Figure 6). There is a bilateral fixed flexion deformity of both his elbows of 50°. As for the range of motion, the patient has got universal restriction of hip motion. Knee extension of up to 5° is possible, and both ankles are fused in plantigrade position. There is a restriction of internal rotation of both his shoulders with the other movements relatively spared. Wrist movements are present but complete range is not possible. The patient has similar deformities of the toes that is bilateral hallux valgus with short great toes (brachydactyly) (Figure 2).

Case 3
The patient’s sister is an 11-year-old female (2nd child) with normal birth history. The patient also has similar deformities of the toes (brachydactyly and hallux valgus) with clinodactyly in fingers of both her hands (Figure 4). The patient has mild mental retardation but did not have any history of birth injection/central nervous system infections. On examination, the patient has an equinovarus deformity of right ankle and foot which is passively correctable. There is equines deformity of her left ankle which also is correctable. There is tautness of both her tendoachilles along with spasticity of both her knees and hips. In upper limbs, there is fixed pronation deformity of her right forearm in 45° with further pronation of 20° possible. There is isolated calcification noted over dorsal aspect of her right wrist. The tone in upper limbs noted is normal with passive range of motion of other joints in both her upper limbs being normal. Paraspinal nodules can be observed and muscles have firm to hard feel on palpation with grossly restricted forward flexion (Figure 7). The patient’s mother and her younger

Figure 1: The index case (17 years/F)

Figure 2: Phenotypic pointer of FOP and its hereditary transmission
couple had few visits for the father's increasing pain and stiffness after marriage and between each of their childbirth, but were not warned of the disease nature or its transmission to their children.

**Follow-up and Management**

As soon as FOP was diagnosed in our index case, the other 2 patients of the family were diagnosed by history and investigations. All three patients were admitted and the index case was started immediately on non-steroidal anti-inflammatory drugs (NSAIDS) and analgesics. Since the other 2 cases did not have any acute symptoms of muscle pain, they were not started on any medications. No invasive procedures or Intramuscular (IM) injections were done in our cases as they are known to cause flare up’s. All three patients were started on gentle physiotherapy and exercises. The parents were explained about the disease, its course and prognosis clearly and the importance of regular physiotherapy and exercises were stressed to them. They have also been stressed to avoid any injuries, or invasive procedures anywhere in future. NSAIDS decreased pain in our index case and by the end of the 1 week her stiffness was less and was able to sit comfortably in bed. And by the end of the 2nd week started to ambulate using walker. In spite of the father's major joints already fused and in established deformity, there was some improvement in him in the form of decreased pain and stiffness. By the end of the 4th week our index case, received in a non-ambulatory state was able to ambulate without support in hand to knee gait. NSAIDS were stopped after 2 weeks when pain was substantially reduced. Patients were followed every month as outpatient and also at 6 and 9 months during which joint deformities were in the same range and there was no worsening of stiffness. Bisphosphonates were not started in our patients as there is no proven evidence of their benefit, and their requirement of long-term usage and its complications.

**DISCUSSION**

In our study, we have described a familial inheritance of FOP which is a rare genetic disorder first described by Patin in 1648 and is characterized by progressive extraskeletal ossification associated with congenital malformation of the great toes, thumbs, hips, and cervical spine. In this family, two daughters and their father were affected with this disease, characterized by fixed flexion deformities, calcifications, and other bony deformities. However, all of them were asymptomatic in the beginning of their life and the symptoms started spontaneously without any history of trauma. Kaplan et al., and Delatycki and Rogers proved that the disease shows autosomal dominant inheritance and some of the cases occurred by new genetic mutations. In spite of extensive literature review, there has not been any documentation of a familial manifestation of this disease.
disease affecting three persons in a row within a family in the Asian region in literature. The diagnostic triad for this disease consists of radiographic abnormalities of the hands or feet; progressive heterotopic endochondral ossification of skeletal muscles, tendon, and fascia; and a pattern of involvement that progresses from axial to appendicular, proximal to distal, and cranial to caudal. Increased heterotopic bone formation may be initiated in response to local trauma (which many times will be so trivial that patients may not give any history of trauma unless persistently asked and stressed about it), and extraskeletal ossification can lead to severe contractures and patients with this disease have bilateral involvement of muscle, tendons, and ligaments and a predominantly endochondral pattern of ossification. There was always some periods of remission and exacerbation but generally it has been agreed that the disease is gradually progressive. Many modalities of treatment have been tried like corticosteroids, mast cell inhibitors, cyclooxygenase-2 inhibitors and NSAIDs, aminobisphosphonates, muscle relaxants, chemotherapy agents, and radiation therapy, bone marrow transplantation, rosiglitazone, retinoic acid receptor agonists and they have produced short term benefits especially in flare-ups but no long-term study has been conducted to establish any of them as a curative modality of treatment and of course all these treatments aspects has got its own adverse effects.

An international panel of physicians has updated the current treatment protocol in FOP where the drug has been classified into one of three categories based on the experimental experience as well as knowledge of each drug’s safety profile.

Class I: Symptomatic treatment with corticosteroids and NSAIDs, cyclooxygenase-2 inhibitors.

Class II: Medications that have theoretical application to FOP, with limited and well-described effects like Leukotriene inhibitors, mast cell stabilizers, and amino bisphosphonates.

Class III: New drugs under investigation suggested are signal transduction inhibitors, monoclonal antibodies targeting ACVR1, and retinoic acid receptor gamma agonists.

In general, the patients should be advised like avoidance of soft tissue injuries, involvement in sports activities and overstretching of soft tissues. The surgeon should avoid biopsies, surgical removal of heterotopic bone, IM injections, and all non-emergent surgical procedures as well as passive range of motion. The physician should avoid all IM immunizations and traumatic Intra venous (IV’s) and arterial punctures. FOP is a condition of considerably reduced lifespan, with the most common cause of death being cardiorespiratory failure from thoracic insufficiency syndrome.

This study shows a familial presentation which is not the usual presentation in this disease.

Authors Suggestions to Doctors and Health Care Officials on Attending the FOP Patient

- A high index of suspicion required on seeing a patient with multiple hard nodules and progressive stiffness and family history is mandatory to identify other patients in the family
- Look for the phenotypic pointers, i.e., bilateral great toe deformity and clinodactyly, if present FOP should be the first differential diagnosis
- Avoid any invasive procedures including IV access or IM injections and strictly instruct patients to avoid any injuries including trivial trauma
- If the patient is in middle age, advice patient to refrain from producing children as this disease still has no treatment or cure and child may face same situation like parent
- If patient presents in acute inflammatory stages, start immediately with NSAIDS and patients should be started on physiotherapy
- Aggressive or passive physiotherapy should not be done as they lead to muscle tears which heals with ossification and aggravating condition
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- Musculo-skeletal tumors can masquerade as FOP and vice versa. Hence, always remember to investigate further clinic radiologically strictly avoiding biopsy until FOP is ruled out
- Refer to higher center or a musculoskeletal specialist.

CONCLUSION

Though FOP is currently an incurable disease, early diagnosis and proper management coupled with creating awareness to the affected individual and his caretakers and with proper physiotherapy, the quality of life of the patient can be grossly changed helping him to live a reasonably good quality of life. FOP is a disease of severe morbidity and mortality at an early age. Hence, genetic counseling is a very important for any affected individual. Early diagnosis and intervention, even though will not change the final outcome that is death due to cardio-respiratory insufficiency, but it will definitely alter the course of the disease and decrease the morbidities and prolongs survival period, thereby giving the patient a good quality life.

REFERENCES


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