FIBRODYSLASIA OSSIFICANS PROGRESSIVA - DIAGNOSIS AND REHABILITATION CHALLENGE
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Abstract: INTRODUCTION Fibrodysplasia ossificans progressiva (FOP) is a rare genetic condition, characterized by congenital malformation of the great toes and progressive heterotopic ossification of connective tissue. Most patients with FOP are misdiagnosed early in life before the appearance of heterotopic ossification and undergo diagnostic procedures that can aggravate the disease process causing lifelong disability. They may become wheelchair bound by the third decade of life.

CASE SUMMARY
A 28 year old female presented with progressive disability and congenital shortening of proximal hallux. She had a fused spine and a fixed pelvis, with fixed flexion deformity of the hips and knee. Her upper limb mobility was severely restricted with fused shoulders and fixed deformities in both elbow joints. She was unable to attain sitting posture for the last seven years and was totally dependent for all activities of daily living (ADL). She has undergone alternative therapies without much improvement and the disease condition had worsened. Even though she sought medical help from an early age, appropriate diagnosis was not made. After presentation to us, clinical diagnosis of Fibrodysplasia ossificans progressiva was made and confirmed with genetic testing. She was offered every three monthly regimen of the Bisphosphonates. She was provided with seating modifications of commercially available wheelchair and aids to maximize her independence in activities of daily living. There is significant reduction in the progress of her deformities and appearance of new areas of ossifications. Now she is an active earning member of her family.

DISCUSSION FOP is a severe progressive disabling condition. Misdiagnosis occurs in about 90% of early cases. The difficulties of a clinician in FOP include proper diagnosis, preventing iatrogenic hazards and treating the condition which has no proven effective therapy till date. The greatest challenge is to rehabilitate these individuals especially with advanced FOP in which all the major joint movements are severely restricted. CONCLUSION Early diagnosis and appropriate physiatric interventions will enable most of the individuals with FOP to have a better quality of life and lead a productive life despite of the severe progressive disability.

Keyword: Fibrodysplasia ossificans progressiva, Heterotopic ossification, Rehabilitation.

INTRODUCTION
Fibrodysplasia ossificans progressiva (ORPHA337; ICD-10 -M61.1) is a rare genetic disease characterized by congenital toe abnormalities and progressive ossification of connective tissue. Fibrodysplasia ossificans progressiva (FOP) has a prevalence of one in 2 million worldwide. It doesn’t have any geographic, gender or racial preference. The ossification occurs in an episodic manner with most patients being confined to wheelchair by the second decade of their life.

CASE SUMMARY
A 28 year old female presented with inability to attain sitting posture. She had severe disability with fused spine, and fixed flexion deformities in her shoulders elbows, hips and knees. Her gait pattern was very energy consuming and slow.

Fig 1
She had congenital shortening of proximal hallux (Fig 1). At 6 yrs of age she had a fall following which she developed small, painful rubbery swelling in the cervical and thoracic paraspinal regions. Subsequently she had restriction of neck movements with palpable hard swellings. She developed multiple similar episodes involving the shoulder, hip, elbow and knee.

Fig 2 & 3
Presently she has scoliosis, her neck and spine are fused, bilateral shoulders adducted and fixed, right elbow is fixed in 130 degrees of flexion, left elbow range of motion is 20-40 degrees. (Fig 2-4)

Fig 4
Her left hip is fixed in neutral position, in her right hip 25 degrees of flexion is possible. (Fig-5) Her right knee has range of movement of 0-20 degree flexion and left knee 10-35 degree flexion. Her jaw movements are severely restricted. Her radiological imaging (Fig 3, 5, 6, 7 & 8) revealed extensive heterotopic ossifications with bony plates along the connective tissues connecting skull to spine, thorax to spine, and ankylosis of multiple large joints. She was prescribed a wheelchair has improved from totally dependent to moderately dependent in daily activities of daily living. Her ICF score after training of daily living. She has been prescribed modified aids and NSAIDs along with calcium and vitamin D supplementation.

Fig 5
Clinical diagnosis of Fibrodysplasia ossificans progressiva was made. Mutational analysis study was done which revealed heterozygous missense point mutation in ACVR1 gene, confirming the clinical diagnosis.

Fig 6 & 7
She was medically managed with a multidisciplinary approach. She was given intravenous Injection Pamidronate once in three months. Short course of steroid was administered for managing acute flare up. She was prescribed on mast cell inhibitors and NSAIDs along with calcium and vitamin D supplementation.

Fig 8
She was given training to maximize her independence in activities of daily living. She has been prescribed modified aids and appliances for activities of daily living. Her ICF score after training has improved from totally dependent to moderately dependent in feeding, brushing and dressing. She was prescribed a wheelchair chair with customized cushion. She was trained to use incentive spirometry to prevent severe restriction in lung volumes. She is under regular follow up.

DISCUSSION
Fibrodysplasia ossificans progressiva is a severely disabling condition. The classical features of FOP are progressive heterotopic ossification with toe abnormalities. The ossification first involves the dorsal, axial, cranial, and proximal regions of the body and later ventral, appendicular, caudal and distal regions. Children are asymptomatic at birth except for congenital malformation of great toes. The variations seen in toes are short hallux with or without clinodactyly. During the first decade of life, they develop sporadic episodes of soft tissue swellings of connective tissues like skeletal muscle, fascia, ligaments, tendons and joint capsule, which are gradually replaced by endochondral ossification with sheets or plates of bone which span across the joint. Each flare ups can cause restriction of range motion. The ankylosis of all major joints renders movement impossible. Scoliosis is a common presentation due to asymmetric HO bridging the trunk and pelvis. Another symptom of this disease is kyphoscoliosis and thoracic lordosis. The median lifespan in this group of patients is around 40 years. The routine biochemical evaluations will be within normal limits. Bone scintigraphy can demonstrate early heterotopic ossification. Majority of FOP occurs sporadically, in others it is an autosomal dominant inheritance. The primary molecular pathology in FOP involves the bone morphogenetic protein (BMP) signaling pathway. It is associated with a mutation in activin receptor Ia/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (MP) type I receptor. (3) The overactive BMP signaling pathway is the underlying cause for ectopic chondrogenesis, osteogenesis and later joint fusions. The inflammatory component of immune system is involved in the pathogenesis of FOP. Genetic testing is available to confirm the diagnosis.

ROLE OF A PHYSIATRIST
Proper diagnosis: In this case, a physiatrist is the index consultant. Considering the fact that it is a very rare disease, the physiatrist plays a central role in the diagnosis. Misdiagnosis can be inadequate. The misdiagnosis of FOP approaches 90 per cent of affected individuals worldwide. (3) Bilateral great toe anomaly is present in 79 to 100% of patients with FOP. (4) Isolated congenital hallux valgus is much rarer than FOP itself. Therefore clinical suspicion of FOP should be there when any patient presents with congenital hallux valgus. (5)

Preventingiatrogenic hazards: Exacerbations can be either spontaneous or precipitated by trauma such as intramuscular injections, muscle biopsy and surgical interventions. Diagnostic errors or inappropriate interventions like an attempt to remove heterotopic ossification can aggravate the disease process. Hence passive stretching of the muscle, intramuscular injections and surgical interventions are contraindicated in FOP.

Management: Presently there is no proven effective therapy for this progressive disabling condition. Corticosteroids (Prednisone 2mg/kg can be administered as a single daily dose for < 4 days) may be effective if given within 24 hours of flare ups that affect major joints or prophylactically after soft tissue trauma. (1, 6) Once steroids are discontinued NSAIDs along with leukotriene inhibitors may be used symptomatically for the duration of flare up. Bisphosphonates (Pamidronate) may inhibit endochondral skeletogenesis at heterotopic sites and can be given with or without steroids in acute flare up (i/v pamidronate 1mg/kg) for three days not more than 4 times/year. (6) Individuals with FOP can be administered prophylactic influenza and pneumococcal vaccine subcutaneously.

Rehabilitation: FOP is a progressive debilitating condition to the patient as well the family. In advanced FOP almost all aspects of life are impacted. Each episode of ossification has the potential to affect range of motion. (7) The difficulties they commonly come across are ambulation, self care and activities of daily living, education, sexual problems and vocation. Rehabilitative strategies should be tailored to the physical and emotional limitation as well as to the aspirations of individual patients. It has to be cautiously administered since minor trauma and muscle fatigue itself can aggravate the disease. Prevention of soft tissue injury and falls is extremely important. Rehabilitative strategies to prevent cardiopulmonary complications should be adopted.

Mobility challenges: Individuals with FOP can have severe limitations in movements due to rigidity of the whole spine, fused hip joints and compromised upper limbs. FOP patients mostly become wheel chair dependant by second decade of life. In this case, patient was not able to sit for the last 7 years though she could walk with a lot of effort. She had frequent falls due to movement restriction. Being limited by endurance, and unable to ambulate on uneven terrain most of her time she is either lying down, standing.

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A wheel chair with custom made seating system was provided to accommodate her fixed posture. A lapboard provision in the wheelchair was also made, which she found very helpful for writing. With this mobility aid, she has started conducting tuition classes for children and has achieved financial independence.

**Activities of daily living:** In advanced FOP individuals become totally dependent for all activities of daily living. Therapy mostly relies on compensatory strategies and providing aids to preserve functionality and independence.

**CONCLUSION**

Clinical suspicion of FOP should be there when any patient presents with congenital hallux valgus, so that management can be initiated early. FOP can be aggravated with mild trauma. The awareness of this disease is essential to prevent harmful diagnostic testing and treatment procedures. Prevention of iatrogenic harm as well as sensitizing patients on injury prevention strategy is an important aspect of FOP management. Definitive genetic testing is available for FOP and hence this can be diagnosed even before the ectopic ossification occurs; if the clinical suspicion is present. To construct an optimal rehabilitation plan is a challenge in the management of individuals with advanced FOP. Early diagnosis and forming a structured rehabilitation plan will enable most of the individuals with FOP to lead a productive life despite of the severe progressive disability. Appropriate customized physiatric intervention is essential to bring out the maximal potential in persons with FOP.

**BIBLIOGRAPHY**
