



Stoneman Syndrome: A Comprehensive Review

Monika.L*, Karthik Mohandas, Sandra.S

Department of Pharmacy Practice, Mallige College of Pharmacy, Bangalore, Karnataka, India.

*Corresponding author's E-mail: monikalokesh58@gmail.com

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ABSTRACT

Stoneman syndrome also known as Fibrodysplasia ossificans progressiva (FOP), or Munchmeyer disease is an extremely rare autosomal dominant genetic disorder of connective tissue caused by heterozygous missense mutation in the bone morphogenetic protein (BMP) type I (Activin A receptor, type I [ACVR1]) leading to secondary skeleton formation, the joints get affected resulting in progressive loss of mobility. The median lifespan of patients suffering from FOP is approximately 40 years of age. Most patients are wheelchair-bound by the end of the second decade of their life and commonly die due to complications of thoracic insufficiency syndrome. There is no effective treatment for FOP; potential treatment may be based on future interventions that block ACVR1 gene. This includes most recent updates in the definition, epidemiology, signs and symptoms, etiopathogenesis, and treatment of FOP.

Keywords: Bone morphogenetic protein (BMP), Heterotopic ossification, SMAD, Activin A receptor type I [ACVR1] gene mutation.

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INTRODUCTION

Stoneman syndrome also known as Fibrodysplasia ossificans progressiva (FOP), or Munchmeyer disease, is a sporadic autosomal dominant disorder of connective tissue caused by heterozygous missense mutation in the bone morphogenetic protein (BMP) type I (Activin A receptor, type I [ACVR1]).^{1,2,3} Most cases of FOP is due to single amino acid substitution, R206H, in the type I BMP/TGF- β cell surface receptor ACVR1 (also known as ALK2), which over-activates signalling through R-Smad1/5/8.⁴ Leading to progressive heterotopic ossification (HO).^{5,6} There is no effective treatment for FOP; potential treatment may be based on future interventions that block ACVR1 gene.

Epidemiology

FOP is an extremely rare genetic disorder with a worldwide prevalence of approximately 1 in 2 million populations. It affects all ethnicities, has no ethnic, racial, gender or geographical predisposition.⁷ Often occurs sporadically and is autosomal dominant trait transmitted with variable expression.⁸ The disorder develops postnatally in the early life, and progresses unavoidably.

In 2007, Ministry of Health, Labor and Welfare of Japan considered FOP as one of the intractable disorders. Individuals suffering from the disease are short lived with a median lifespan of about 40 years of age.^{9,10}

Etiopathogenesis

FOP is an autosomal dominant disorder (i.e., can be inherited by either parent), caused due to heterozygous missense mutation of ACVR1 gene. However, most of the cases arise sporadically as a result of new mutation.¹ This mutation causes substitution of codon 206 from arginine to histidine in the ACVR1 protein, resulting in abnormal activation of ACVR1, leading to the transformation of connective tissue and muscle tissue into a secondary skeleton, as many tissues of the body including cartilage and skeletal muscles contains ACVR1 protein, responsible for controlling the growth and development of the muscles and bones, including the gradual replacement of cartilage by bone (ossification) that occurs in normal skeletal maturation from birth to young adulthood. This causes endothelial cells to transform to mesenchymal stem cells and then to bone.⁴

Molecular basis of disease

Bone morphogenetic protein (BMP) receptors are serine-threonine kinase receptors. TGF- β family proteins bind to these receptors and help in paracrine signalling. ACVR1 is a type of BMP receptor encoded by ACVR1 gene. In 2006, it was identified that Arg206His (R206H) ACVR1 gene mutation was responsible for FOP.¹¹ R206H mutation causes ligand independent BMP signalling and increases BMP responsiveness by increasing SMAD1/5/8 signalling.

BMP receptors

BMP receptors are type of TGF- β super family receptors. There are mainly four types of BMP receptors namely BMP type1, ACVR1, BMPR1A, BMPR1B, BMP type2. ACVR1 is a type of BMP receptor; these are serine-threonine kinase receptors.¹²



ACVR1 signalling and transcription

When ligands (various growth factors act as ligands for BMP receptors) bind to ACVR1 receptors, intracellular signalling is regulated by regulatory molecules known as receptor regulated SMAD (R-SMAD), these are transcriptional factors that transduce extracellular ligand signalling from cell membrane bound ACVR1 receptors into nucleus where they activate transcription of ACVR1 target genes.¹³ There are several SMAD molecules which are been signalled by different signalling molecules, namely SMAD1/2/3/5/8 these are R-SMAD's and SMAD4 also known as common partner SMAD (Co-SMAD), help in carrying out intracellular signalling when R-SMAD's are activated. I-SMAD's also known as inhibitory SMAD's (SMAD6/7) compete with SMAD4 and affect the modulation of ACVR1 regulated transcription.

TGFβ superfamily receptors have two monomeric receptor subunits, TGFβ type 1 monomer and TGFβ type 2 monomer. Type 2 monomers have extracellular cysteine rich domains for binding of ligands, on binding of ligands to type 2 receptor causes dimerization of type 2 receptors,

signals recruitment of type1 receptors, due to kinase activity of type2 receptors phosphorylates serine residues of intracellular domain of type1 receptors forming a heterotetrameric complex, recruits R-SMAD's, bind to tetrameric complexes at L-45 region of type1 receptor. Recruitment of R-SMAD is facilitated by special proteins called SARA, which anchors cell membrane and helps R-SMAD's to bind to type 1 receptors. Due the kinase activity of type1 receptors phosphorylates R-SMAD's, causing conformational change at their MH2 domain (activated R-SMAD). Activated R-SMAD's signals binding of Co-SMAD, forms R-SMAD Co-SMAD Complex that transcribes the genes that regulates osteogenesis, neurogenesis and ventral mesoderm specification.^{4,14} [Figure 1]

Activin-A is a ligand for TGFβ receptors, these receptors mediate intracellular signalling via SMAD2/3, but in R206H mutation activin-A stimulates SMAD1/5/8, enhances endochondral ossification and chondrogenesis (i.e., ligand independent BMP signalling). Resulting in secondary skeleton formation (heterotopic ossification) in the soft tissues limiting the mobility.

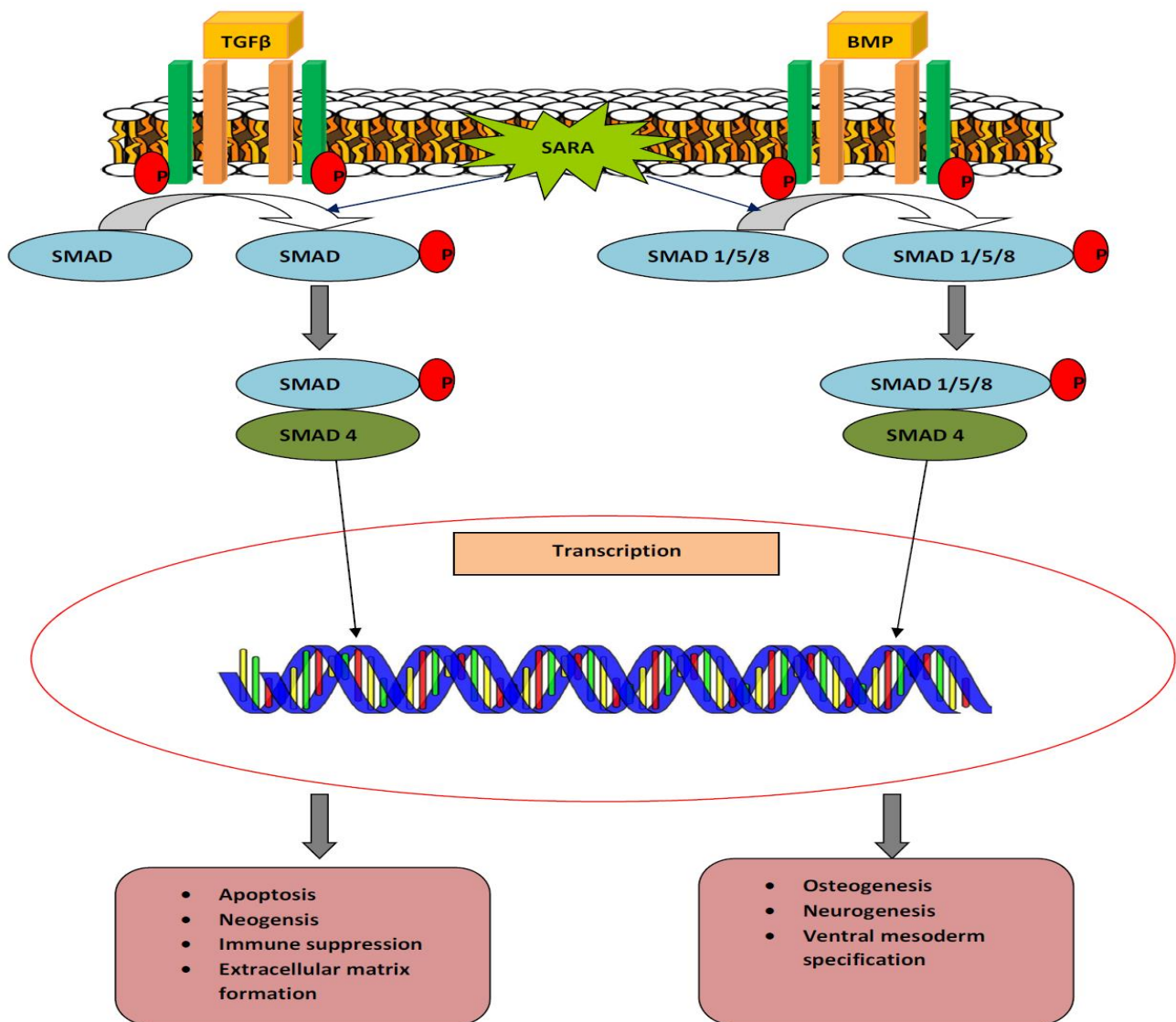


Figure 1

Signs and symptoms

The disease condition is characterized by abnormal ectopic ossification of the tendons, ligaments, skeletal muscles, and other soft tissues of the body.¹⁵ This process generally becomes noticeable in early childhood; the bone growth generally progresses from the top of the body downward, just as bones grow in fetuses starting with the neck and shoulders and proceeding down the body and into the limbs.¹⁶ As a result of secondary skeleton formation, the joints get affected leading to progressive loss of mobility. Inability to fully open the mouth may cause difficulty in speaking and eating because of which people with this disorder may experience malnutrition due to their eating problems. They may also experience difficulties in breathing as a result of HO around the rib cage, restricting the expansion of the lungs and diaphragm causing respiratory complications.^{15,16} Hardening of soft tissue, pain and swellings over the affected muscles are some of the initial symptoms of FOP which finally leads to ossification. It usually occurs from birth to the second decade of life, following spontaneous or trauma-induced flare-ups.⁷ Later progression of disease occurs in the appendicular, ventral, distal and caudal regions. However, order of occurrence of disease may vary due to injury-caused flare-ups. Often, the tumour-like lumps that characterize a flare-up of the disease appear suddenly and sometimes due to unknown reasons, children born with FOP may have a notable lump at the minor joint or missing joint or malformed big toes.¹⁵ The common cause of death in this condition is due to cardiac and respiratory failure which results due to severe restriction of chest wall movements.¹

Diagnosis

FOP is a rare and disabling disorder that still does not have an effective treatment that can cure it or stop its progression.⁷ Clinical suspicion of FOP in the early life is based on malformed great toes that can help in early clinical diagnosis and treatment by preventing harmful consequences at later stages.¹⁷ Diagnosis is mainly based on the radiographic imaging findings. The abnormal bone scans detect heterotopic ossification. Magnetic resonance imaging also helps in early diagnosis before ossification; early diagnosis is beneficial in avoiding the unnecessary invasive investigations like biopsies and intramuscular injections which would exaggerate progression of the disease condition with inflammation. Hence, proper knowledge of this disease condition is very important for radiologists to avoid such invasive investigations.¹ Palpation reveals the tenderness of all visible masses and stiffness of all the abdominal and paraspinal muscles.⁷

Major criteria for diagnosis of FOP

- Progressive heterotopic endochondral ossification
- Congenital malformation of great toes
- Disease progression with well-defined anatomical and temporal patterns

Laboratory tests

Show discreet increase in the erythrocyte sedimentation rate and routine biochemical evaluations of bone mineral metabolism are usually normal, although serum alkaline phosphatase activity may be increased especially during disease flare-ups. Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibroproliferative lesions.¹⁸

Genetic analysis

Analysis of ACVR1 gene mutation is the confirmatory test.

Imaging examinations

Imaging examinations such as radiography and computed tomography showing heterotopic bones confirm the diagnosis.⁷ Radiographs of the neck, chest, and feet can reveal multiple ectopic osseous growths in the soft tissues of posterior aspects of neck, chest, and abdominal wall. Radiographs of foot may show bilateral hallux valgus deformity, monophalangeal great toe, short first metatarsal with normal cervical vertebral bodies and posterior elements giving a strong suspicion of FOP and the radiographs of hands and knee may show short first metacarpals with bilateral and sharp bony outgrowths in medial aspects of tibia, referred to as pseudo exostoses due to their close resemblance to osteochondromas (exostoses).¹

Characteristic imaging and clinical findings of FOP

- Bilateral hallux valgus deformity
- Monophalangeal great toes
- Heterotopic ossification of muscles and connective tissues
- Short and broad femoral necks
- Short first metacarpal/metatarsals
- C2-C7 facet joint fusion
- Large posterior elements
- Tall narrow vertebral bodies

Wrong diagnosis of FOP is very common but can be avoided by examining individual's toes for the characteristic feature of short great toes. FOP is commonly misinterpreted as aggressive juvenile fibromatosis, dermatomyositis, lymphedema, or soft-tissue sarcoma by the clinicians.¹ FOP should also be differentiated from other genetic conditions of heterotopic ossification (HO), and nonhereditary (acquired) HO. One such condition is progressive osseous heteroplasia (POH), a rare genetic condition of progressive HO defined clinically as cutaneous ossification that usually presents at childhood and progresses with the involvement of subcutaneous and deep connective tissues, including muscle and fascia, in the absence of multiple features of Albright hereditary osteodystrophy (AHO) or hormone resistance. FOP is differentiated from POH by congenital malformation of great toes, with perosseous inflammation



commonly known as “flare-ups” and also the absence of cutaneous ossification.¹⁷ So joint malformations and soft tissue ossification are the characteristic radiographic features of FOP with malformation of the great toes, thumbs, cervical spine and proximal femurs, and presence of proximal medial tibial osteochondromas, can make the diagnosis more certain.¹⁸

Treatment

In FOP the abnormal expression of enzyme used for bone repair by injured tissue and muscle causes lymphocytic recruitment and excessive formation of BMP-4 which results in bone formation.¹⁹ There is no preventive or effective treatment for FOP. Studies are being done to suppress the overactive ACVR1/ALK2 signalling pathway that would specifically block heterotopic ossification. Currently FOP is managed by supportive therapy that is based on the early diagnosis of the condition and avoiding injuries or iatrogenic harm, and providing symptomatic relief in cases of painful flare-ups by conservative use of analgesics, and preserving residual functions, with final option of surgery.^{1,7}

Surgical excision is considered when there is excessive pain, joint limitation, or nerve compression is present. Surgery generally is advised when myositis ossificans is ripe, identified by a higher bone density in x-ray findings and normal erythrocyte sedimentation rate and alkaline phosphatase level.⁷ Corticosteroids are indicated as first-line treatment at beginning of flare-ups. A brief 4 day course of high-dose corticosteroids, started within first 24 hours of flare-up, may help reduce the intensity of inflammation and tissue edema commonly seen in the early stages of the disease. Corticosteroids should be restricted for the treatment of flare-ups that affect jaw or submandibular areas and major joints. Corticosteroids is not generally be used for symptomatic treatment of flare-ups that involve the back, neck, or trunk because of long duration and recurring nature of these flare-ups as it is difficult to assess the true onset of such flare-ups. A typical dose of prednisone 2 mg/kg/day, administered as a single daily dose. If a second course of corticosteroids becomes necessary, this should be followed by a slow dose tapering.¹⁷

In children, restriction of physically interactive play may be helpful to reduce falls. Improvement in household safety, use of ambulatory devices, protective headgear and modification in their activities are some of the strategies to prevent falls and minimize the risk of injury when children fall.¹⁷

Physical rehabilitation focuses on improving daily living activities by approaches that avoid passive range of motion which could lead to disease flare-ups. Occupational therapy and vocational education consultations may be useful approach.^{17, 18}

CONCLUSION

Stoneman syndrome is a rare genetic disorder of connective tissue affecting in the early decade of life, affected individuals experience difficulty in movement and often experience flare-ups that affect their lifestyle. There is no cure to this condition; effective treatment would involve targeting the mutated gene.

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