Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatric Medical Emergencies

Fibrodysplasia Ossificans Progressiva in Children: A Case Report

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DOI: 10.36347/sjmcr.2022.v10i07.035 | **Received:** 13.06.2022 | **Accepted:** 25.07.2022 | **Published:** 30.07.2022

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Abstract **Case Report**

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant genetic disease. The diagnosis is clinical and is based on two criteria: congenital bone deformities of the hands and feet (in particular a bilateral hallux valgus with a monophalangeal appearance) and ossification of the interstitial connective tissue of the striated muscles (spontaneous or triggered by minimal trauma). This irreversible ectopic osteogenesis evolves in bouts, progressing according to a precise anatomical pattern. The hypothesis of a genetic mutation in the BMP4 signaling pathway, responsible for a dysfunction of the immune system, has been evoked for some years. Recently, a gene involved was identified on chromosome 2: it is ACVR1, one of the BMP receptors. FOP is an example of the difficulty of management, since no curative treatment is effective on the progression of the disease; only preventive and conservative management associated with symptomatic treatment of relapses can be proposed at present.

Keywords: Fibrodysplasia, Child, Clinical aspects, Etiopathogeny, Treatment.

INTRODUCTION

Heterotopic ossification is defined as the formation of extra-skeletal bone in soft tissue. This process results from the alteration of the normal regulation of osteogenesis. Heterotopic ossification can vary from a small asymptomatic lesion discovered incidentally on radiography to extensive lesions with major functional consequences, severely impairing quality of life.

COMMENT

Y. Z, female infant, 20 months old, with no particular history, who has had subcutaneous nodosities on the left thigh and right arm since the age of 6 months.

The evolution was marked by the installation of a limitation of the flexion of the left knee and the 2 arms with the appearance of a tumefaction at the level of the back 3 months ago which motivated a consultation with a pediatric surgeon where standard X-rays were requested and a biopsy of the tumefaction of the back was made objectifying a Hamartome.

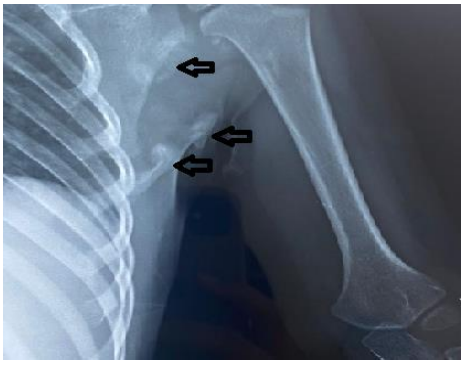
On admission to the pediatric medical emergency department, the infant was conscious, apyretic, hemodynamically and respiratorily stable. On skin and mucous membranes examination, he presented with achromic spots on the right arm, a 1 cm hard painless swelling on the back and forehead, a subcutaneous nodule and a 1.5 cm induration on the 2 arms and left thigh. The joint examination found a limitation of the flexion of the left knee and the abduction of the 2 arms, with a hallux valgus of the 2 big toes. The rest of the examination was unremarkable.

The biological workup, in particular the phosphocalcic workup, came back normal.

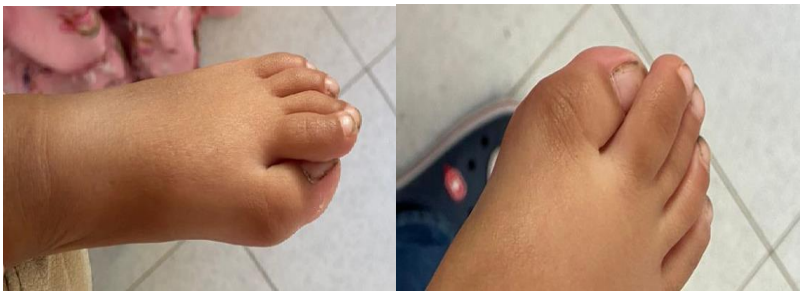
An ultrasound of the soft tissues was performed, showing a bony outgrowth on the right rib and left femur, with doubts about the scapular location, suggesting an exostosizing disease.

The brain, thoracic and 2 lower limbs CT scans were the first to suggest fibrodysplasia ossificans with exostoses.

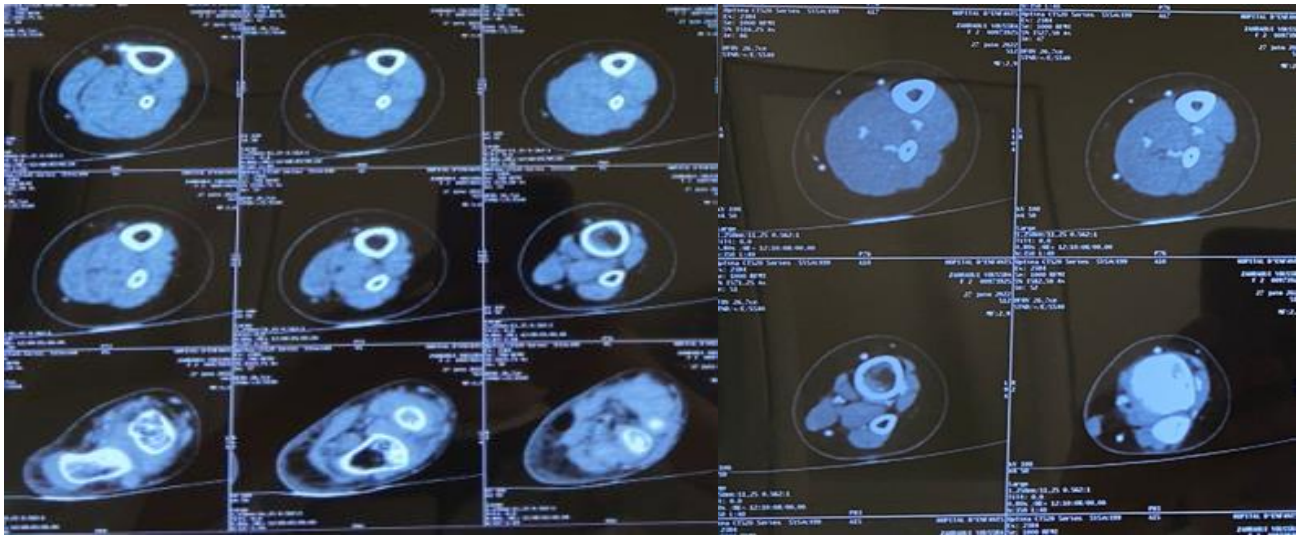
Molecular research was done to identify the ACRV1 gene mutation, which confirmed the diagnosis of fibrodysplasia ossificans progressiva.



Bone Growths



The Two Big Toes an Valgus



Bony Outgrowths with a thin Cartilaginous Cap

DISCUSSION

FOP is clinically characterized by the association of a congenital malformation of the short, valgus deformed big toe with episodes of inflammatory flare-ups leading to the development of heterotopic ossifications in connective and muscular tissues. These flare-ups occur at a variable age, are progressive and cumulative, leading to generalized ankylosis, respiratory and thromboembolic complications and early death in adulthood [1].

The diagnosis of FOP is exceptionally made antenatally. During the first months of life, transient nodules of the scalp may occur, sometimes inflammatory and painful swellings, which disappear spontaneously in a few days, without leaving any sign in the majority of cases [2].

These are painful swellings, sometimes accompanied by general signs (fever), progressing according to a particular pattern (cranio-caudal, posteroanterior and proximo-distal) mimicking the normal development of the embryonic skeleton. In most cases, these painful inflammatory areas give way to localized ankylosis, reflecting the phenomenon of heterotopic endochondral ossification. They generally concern first the cervical and paravertebral regions, then the shoulders, the dorsal and lumbar regions, the hips, and finally the limbs.

The flare-ups may be spontaneous or secondary to a triggering event, such as muscle injury or influenza-like viral pathology: intramuscular vaccination, trauma or muscle hematoma, fall, influenza. Surgical removal of an inflammatory lesion can lead to a series of successive attacks lasting several months. Smooth muscle, cardiac muscle, and certain skeletal muscles such as the diaphragm, periorbital muscles, and tongue are spared [3,4]. Other clinical events mark the evolution of FOP. Children often have a statural advance with advanced bone age during the first 10-15 years, until joint and muscle ankylosis limits their growth. Deafness (sensorineural or mixed) occurs in 50% of cases at late pediatric age [5]. During the second decade, cumulative muscular and periarticular ossifications lead to progressive limitations of walking and daily life gestures, with progressive loss of independence.

Radiologically, the earliest sign is monophalangism of the first toe, associated with a stubby and enlarged appearance of the first metacarpal. The first phalanx is usually short, triangular or trapezoidal, sometimes fused with the first metatarsal or the second phalanx.

In the early years, thin, sessile osteochondromas (or exostoses) appear in the lower femoral and upper tibial regions. An elongated and narrow appearance with fusion of the articular facets of the C2 to C7 vertebrae is frequently observed early on, associated with a limitation of cervical mobility, even before the first attacks appear. Finally, the femoral necks are wide and stocky, contrasting with the small size of the upper femoral epiphyses. The great variability of this condition has long been emphasized. There are forms of early expressivity and others that reveal themselves in adolescence or even in adulthood. Regardless of the age of onset, there are forms that are slowly progressive and others that progress rapidly. The minor signs of classical FOP are present in a variable way (hearing loss, osteochondromes, chronic pain syndrome).

In addition, there are atypical forms of FOP associating original signs such as transverse reduction anomalies, alopecia, ophthalmological damage (cataract, glaucoma) or cerebral anomalies with possible intellectual deficiency [5].

The diagnosis of FOP is suspected on the basis of radio-clinical elements; it is confirmed by a molecular study carried out during a medical genetic consultation, explaining the objectives of the genetic study, including the possibility of adequate genetic counseling. In the majority of cases, it is a single mutation, R207H, in the ACVR1 (ALK2) gene, which encodes the type I receptor for activin A (or activin-like kinase 2), a bone morphogenetic protein (BMP) receptor. Other mutations affecting different domains are described, associated with atypical forms of FOP.

Despite the progress made in understanding the molecular nature of FOP over the last ten years, no effective preventive or curative treatment exists yet.

However, physical therapy with orthotics is indicated to limit progressive stiffening and to maintain joint range of motion.

Patients with FOP should avoid as much as possible any fall, muscle trauma and/or intramuscular injection.

Flu vaccination is strongly recommended. A study conducted in 2000-2001 suggests that influenza infections are triggers for relapses. Indeed, patients with FOP who contract the flu have a 60% probability of developing a relapse compared to only 11% in those who do not contract the flu. Prophylactic vaccination may therefore be a safe and effective way to prevent a flare-up in a FOP patient.

The optimal treatment of FOP is probably based on the knowledge of the cellular and molecular pathophysiology of the disease. These are corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) including anti-COX2. Effective in reducing the edema and pain symptomatic of an acute flare of PFO, their side effects are generally minimal.

Cyclooxygenase-2 inhibitors and NSAIDs specifically targeting pro-inflammatory prostaglandins, anti-COX2 agents have interesting properties for the treatment of FOP. In addition, a study has unexpectedly shown that anti-COX2s have effective antiangiogenic properties.

Other drugs have been proposed and their use is theoretical. These are amino-biphosphonates, leukotriene inhibitors and mast cell stabilizers.

Finally, correction of the gene responsible for FOP would be the treatment par excellence; now that a gene has been identified, this becomes a less utopian hypothesis.

CONCLUSION

FOP is an example of the difficulty of management, since no curative treatment is effective on the progression of the disease; only preventive and conservative management associated with symptomatic treatment of relapses can be proposed at present.

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