ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 01, pp.18315-18320, January, 2018

CASE STUDY OPEN ACCESS

CLINICAL REPORTS OF 31 BRAZILIAN CASE PRESENTATIONS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

[1*]Marilene Garcia Palhares, [1]Deborah Ribeiro Nascimento, [1]Liane de Rosso Giuliani, [1]Paula Cristhina Niz Xavier, [1]Valter Aragão do Nascimento, [2]Almir Sousa Martins and [1]Durval Batista Palhares

[1]School of Medicine – Federal University of Mato Grosso do Sul, Brasil
[2]Departamento de Fisiologia e Biofísica- ICB/Universidade Federal de Minas Gerais, Brasil

ARTICLE INFO

Article History:
Received 18th October, 2017
Received in revised form
07th November, 2017
Accepted 20th December, 2017
Published online 31st January, 2018

Key Words:
Fibrodysplasia Ossificans Progressiva,
Flare up, Ectopic Ossifications,
Hallux Valgus.

ABSTRACT

Fibrodysplasia Ossificans Progressiva (FOP) is a rare autosomal dominant disease, caused by heterozygous mutation in the type I activin receptor gene on chromosome 2q24 that, due to instability, causes progressive ectopic ossification. The objective of the present study was to evaluate the characteristics of 31 patients with FOP from different regions of Brazil. Some characteristics include current age, flare ups, disease progression, *hallux* characteristics, diagnosis, ectopic ossification sites, and symptoms of cramps, temporomandibular joint, dental conditions and previous surgeries. O all patients, 51.6% had *hallux valgus* ,9.7% had *hallux phalanx* absence, 32.2% had both Hallux valgus and Hallux phalanx, and 6.4% had none. The first flare up was around 5 years, occurring more in neck and back and the age of diagnosis around 9 years. Among the families evaluated, three fathers were affected. Most of the patients presented difficulties in walking and some were wheelchair-bound or bedridden. Some patients have auditory deficit and limitation of mouth opening. More than 50% of patients complained of cramps. Different treatments were performed and 4 patients underwent surgery of *hallux valgus* and others underwent other surgeries (45%). The majority of the diagnoses were late.

Citation: Marilene Garcia Palhares, Deborah Ribeiro Nascimento, Liane de Rosso Giuliani, Paula Cristhina Niz Xavier, Valter Aragão do Nascimento, Almir Sousa Martins and Durval Batista Palhares, 2018. "Clinical reports of 31 brazilian case presentations with fibrodysplasia ossificans progressiva", *International Journal of Development Research*, 8, (01), 18315-18320.

INTRODUCTION

The report of these 31 patients is very important, because it shows that patients may present during the course of the disease different clinical manifestations, and some are more likely to present, for example, disorders such as temporomandibular joint limitation, complaints of Cramps have been frequent, not yet mentioned in other articles, in addition to many patients end up having worse prognosis in the long term due to iatrogenies. Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disease, occurring in the world from 1 case to 2 million people, whose muscular and connective tissues (ligaments and tendons) are gradually being replaced by bone tissue.

Corresponding author: **Marilene Garcia Palhares,**
School of Medicine – Federal University of Mato Grosso do Sul, Brazil.

With the evolution of the disease, the patient has limited movement, going to a wheelchair or a bed, with difficulty feeding due to the ossification of the temporomandibular joint, and even limiting his own hygiene (Ahn *et al*., 2003). In the literature, the first case report is from Patin, in the year of 1692 (Patin *et al*., 1992). Patients with FOP have a mutated version of the BMP receptor type I (T1-BMPR) ACVR1 / ALK2), which causes heterotopic bone at muscle injury sites (Shore *et al*., 2006). Individuals with FOP appear normal at birth, except for changes in halux: usually deviated and monophalangeal. Patients with FOP may present flare-up or a sudden worsening of symptoms, whose flare-up may be predisposed by any trauma to muscles or connective tissues. If a patient with FOP experiences a fall, for example, it can trigger episodes of muscle swelling, followed over time by ossification development in the affected area.

Diseases such as influenza, infectious diseases in general, intramuscular injections, mood disorders, may also trigger disease crises (Kaplan *et al*., 2009; Palhares & Leme, 2001; Kaplan *et al*., 2008a). FOP to date does not have an effective treatment. Many authors have suggested some treatments (Palhares & Leme, 2001; Palhares *et al*., 1997; Kaplan *et al*., 2013; Palhares *et al*., 2010; Weiss, 2010). Corticosteroids are sometimes prescribed in acute attacks. The objective of this study was to know the different characteristics of 31 patients from different regions of Brazil, different ages and their various clinical manifestations.

Case Presentation

Fop is a disease that in most cases, the first flare-up occurs before the age of 10, with the presence of hallux valgus and many patients may present the absence of phalanx (Table 1).
Case Presentation Thirty-one patients with fibrodysplasia ossificans progressiva, all from Brazil, and different regions were evaluated.

All patients or caregivers signed the Free and Informed Consent Form, regardless of age. Those under 18 years of age and older than 6 years of age agreed to the study by signing the Free and Informed Consent Form, in addition to those responsible for signing the TCLE (Brazilian Platform - Ethics Committee, CAAE: 60117916.0.0000.0021). A card with numerous questions was asked for each patient or caregiver, such as age, presence of *hallux valgus*, absence of *hallux phalanx*, age of first flare-up, age of diagnosis and whether other family members are affected. In another record, other questions were asked, the location of the first flare up, the current physical situation, the site of greater ossification, hearing condition, whether the temporomandibular joint is normal or limited, the dental situation, if the patient was submitted to any FOP-related surgery or not. All of these questions are in tables in the results.

Clinical Findings, timeline, and diagnostic Assessment

The personal characteristics of the 31 FOP patients are in Table 1. In Tables 2 and 3, are reported other characteristics of the 31 patients. Table 1 shows the average of chronological age of the 31 patients with FOP, which was 20 years old, and the ages ranged from 7 to 52 years old. Of the 31 patients, 26 had bilateral *hallux valgus*, and of these, 13 had bilateral *hallux* absence of the phalanx. The median age of the first flare-up was five years, ranging from 12 days of life to 20 years of age.

Table 1. Personal characteristics of Fibrodysplasia Ossificans Progressiva patients (n=31)

Identification	Current AGE	Hallux valgus	Hallux phalanx Absence	First Flare up (Y/MO)	Age diagnosis	Other affected family members
IVA	11	Yes	-	3	03	-
DCA	14	Yes	Yes	2 / 5	2.9	-
AGP	32	Yes	-	2 / 6	Newborn	-
DVOB	7	Yes	-	6	06	-
MAAP	7	Yes	Yes	6 / 4	06.4	-
RSMF	27	Yes	-	0 / 8	14	-
VADF	29	YeS	-	5	06	F/B
CA	34	Yes	Yes	1 / 8	23	-
GSL	30	Yes	Yes	5	07	-
KCGS	41	Yes	Yes	7	29	-
RHNB	31	Yes	-	16	10	F
FJMS	54	-	-	20	16	-
CNE	14	Yes	-	8	12	-
WRMS	19	Yes	-	2	05	-
GLG	22	Yes	-	2 / 6	2.4	-
EPGC	12	Yes	Yes	9	09	-
ADFN	28	Yes	-	6	06	F/B
RJB	14	Yes	Yes	5	07	-
GSK	17	Yes	-	11	11	-
GDF	19	-	-	16	16	-
ESG	28	Yes	Yes	5	27	-
PERS	7	Yes	Yes	0 / 7	02	-
AD	30	Yes	-	5	13	-
LFPM	22	Yes	-	3	7	-
ABP	12	-	Yes	6	11	-
MMCSP	52	-	Yes	4	48	-
VEO	7	Yes	-	3	06	-
CQC	21	Yes	Yes	6	08	F/S
FAOS	20	-	Yes	5 /10	08 10M	-
HSRB	7	Yes	-	12 days	04	-
CVAO	13	Yes	-	0 / 5	01 7M	-
Mediana	20 Y			5	9	n = 28 F =3 S = 1 B = 2

Abbr: (Y/MO) years/months; (F) FATHER; (B) BROTHER; (S) SISTER; n= no one

The median age of the diagnostic suspicion was 9 years, varying from the neonatal period up to 52 years of age. Of all the patients evaluated, 27 corresponded to new mutation and in 4 patients (two were siblings), 3 fathers were affected with FOP (Table 1). In Table 2, the location of the first flare-up was reported, with 35.48% being the neck, 32.26 in the back, 12.90% upper limbs, 6.45% lower limbs, and 3.23% head, hip and feet, each one.

Table 2. Other clinical characteristics of Progressive Ossificans Fibrodysplasia patients analyzed (n=31)

Identification	1st flare-up location	Current physical situation	Highest ectopic ossification site	Hearing	TMJ (% locked)	DS	PS
IVA	Neck	W	Back	N	N	G	No
DCA	Back	W-LL	Back	N	N	NT	Yes*
AGP	Neck	Bedridden	Back	N	N	G	No
DVOB	Neck	W-L	Back	D	N	NT	Yes
MAAP	Neck	W-L	Back	N	N	G	No
RSMF RAIMU	Head	Wheelchair	thigh	N	N	NT	No
VADF	Neck	W-L	Back	N	D 80%	NT	No
CA	Neck	W-L	Arms	D	D 40%	G	No
GSL	thigh	Wheelchair	Back	N	D 80%	NT	No
KCGS	Back	W-L	Hip	N	N	G	No
RHNB	Back	W-L	Back	N	N	G	No
FJMS	Back	Bedridden	Back	N	D 100%	NT	Yes
CNE	LM	W-L	LM	N	N	NT	Yes
WRMS	Neck	W-L	Back	N	N	G	biopsy
GLG	Neck	W-L	Legs	N	D 20%	NT	Yes
EPGC	UL	W	LM	N	N	G	No
ADFN	Back	W-L	Back/Femur	N	D 100%	B	No
RJB	Back	W	Back	N	N	G	No
GSK	UL	Walk-LL	Back	N	D 20%	G	Yes*
GDF	LM	W-LL	ankle	N	N	G	No
ESG	Back	W-L	Back, arms	N	N	NT	No
PERS	LM	W-L	Back	N	D 40%	G	Yes
AD	Neck	Wheelchair	Back	D	D 80%	NT	No
LFPM L	Back	W-L	UL	D	D 80%	G	biopsy
ABP	Feet	W	Feet/legs	N	N	G	Yes
MMCSP	LM	W-L	Kn / hands	D	D 60%	G	Yes**
VEO	Hip	W	Back	Deaf	N	NT	No
CQC	Back	Bedridden	Back	N	N	G	No
FAOS	Neck	W-L	Back	D	N	G	No
HSRB	Neck	W	Back, Arms	N	N	G	No
Cvao	Back	Bedridden	Back, PR	N	D 80%	G	No

Neck =12; Back =10; Head=1; Hip=1;LM =3 ;Feet=1 ; UL=2;Tigh=1. *Abbr:* Bad: bad. Yes** = Surgery not related to the disease.D = decreased; Difficulty (%) = D; DS: Dental situation; Good = G; Kn: Knee; LM: lower members; Normal = N; NT: Need treatment; PR = Pectoral region; PS: Previous surgery (hallux, ectopic bone); TMJ = Temporomandibular joint.; UL: upper limbs; W= walks; Walk-L: walk limitation; WL: Walks with limitation; WLL: Walks with little limitation;

Table 3. Clinic of cramps, treatments previously received, surgical and diagnostical characteristics of the 31 patients studied

Identification	Chambers	Treatment	surgery procedure	DIAGNOSIS
IVA	No	CST, AI, MS	None*	XR
DCA	No	AI, BPT, VC	Toes**	XR,
AGP	No	CST, AG, BPT,VC	None	Clinic
DVOB	Yes	CT, AG, AI, MS	Toes, Biopsy***	Clinic, XR
MAAP	No	CST, AG, AI	None	Clinic, XR
RSMF	No	CST, AG, AI	biopsy	Clinic
VADF	Yes	CST	None	Clinic
CA	No	AI	None	Clinic
GSL	Yes	CST, AG, AI	None	Clinic
KCGS	Yes	CST	None	XR
RHNB	No	CST, VC	None	Clinic
FJMS	No	AG, AI	REB	Clinic
CNE	No	AG	FC	Clinic, DNA. XR
WRMS	Yes	CHT	Biopsy	Clinic, DNA
GLG	Yes	BPT	REB	Clinic, XR
EPGC	No	CST, AI	None	Clinic, DNA
ADFN	Yes	Homeopathy	None	DNA,
RJB	Yes	MS	Toes	XR
GSK	Yes	CST, AG, AI	Toes	Clinic, XR
GDF	No	CST, AG, AI	DS	XR
ESG	Yes	CST, AG, ACPT	Toes	XR
PERS	Yes	CST, AG,AI	IH	XR
AD	Yes	CST,	None	Clinic
LFPM	No	CST, AI.	biopsy	DNA, XR
ABP	Yes	CST,	None	Clinic, DNA, XR
MMCSP	No	CST, AG, AI	CS	Clinic, DNA
VEO	Yes	CST, AG, AI	None	Clinic, XR
CQC	Yes	CST	None	Clinic, DNA, XR
FAOS	No	CST, AG,AI, OT	None	Clinics, XR
HSRB	No	CST, AG, AI	None	Clinic, XR
Cvao	Yes	CST, AG, AI	None	DNA,

*None: 17; **Toes: 4; ***biopsy: 4; Others: 7. Abbr: ACPT = Acupuncture; AG = Analgesics; AI = Anti-Inflammatory; BI = Breast Implants; BPT = Bisphosphonates ; CHT =Chemotherapy; CS = Caesarean section; CST: Corticosteroids ; DNA = Sequencing DNA.; DS = Dental surgery; FC = Fracture Correction; IH = Inguinal hernia; MS = Montelukaste sodium; OT = Others; XR = X-ray; REB = Resection of ectopic bone; VC = Vitamin C.

Therapeutic Intervention

In Table 3, are some other data referring to the 31 patients with FOP. Frequent complaints were reported in 16 (51.61%) of the 31 patients. All patients had previous treatment, 14 (45.16%) used corticosteroids, 17 (54.84%) reported on the use of nonsteroidal anti-inflammatories, 16 (51.61%), analgesics, bisphosphonates and ascorbic acid in 3 (9.68%) cases, Montelukaste Sodium 2 (6.45%) cases and 1 (3.23%) reported acupuncture, also 1 (3.23%) had treatment with homeopathy and 1 (3.23%), used unspecified natural medicines . Regarding previous surgical procedures, in 17 (54.84%) patients there was no report of previous surgical intervention. As for the initial diagnosis, in 8 patients, the suspicion of FOP was only clinical. In 9 cases, the diagnosis was confirmed by DNA sequencing of the ACVR1 receptor. In 6 patients, besides DNA sequencing, the diagnostic confirmation was also clinical and x-ray.

DISCUSSION

According to the incidence of patients with FOP in the population, 31 cases possibly refer to an approximate population of 62 million people. Considering that Brazil has a population of approximately 210,000,000 people, thus, in this country it must have at least 105 patients with FOP, but many of them, especially in less favored regions, may be without a diagnosis for life, or not have it, until he has the opportunity to be consulted by a more experienced professional. The mean age of the patients in this study was 20 years, ranging from 7 to 54 years of age (Table 1), but a very short lifespan Kaplan *et al*., 2010). Of this population, 26 patients presented bilateral *hallux valgus* (83.87%) and the absence of the *hallux valgus* phalange in 13 (41.93%) cases. *Hallux valgus* has clinical importance of recognition and correlation with FOP, already in the neonatal period. Although there is no established treatment, preventive measures throughout life are important in the prognosis, because preventive measures, such as intramuscular vaccines, surgeries, etc., can improve the patient's prognosis in the long term. Drastic measures such as correction of *hallux valgus* itself may be a flare-up factor and subsequent formation of heterotopic bone (Singh *et al*., 2016).

Thirteen patients (41.94%) had absence of hallux phalanx, as reported by other authors (Ulusoy, 2012; Hasan, 2012). It has also been reported patients with FOP and no characteristic skeletal abnormalities (Ulusoy, 2012; Hasan, 2012) as observed by 3 (3.23%) patients of the 31 of this study. Although some patients had their first flare up after 16 or even 20 years of rest, most were before the 5th year of life. The first flare ups have been reported in the first decade of life (Cohen *et al*., 1993). Smith and collaborators (1976), observed that in a study with 28 patients, heterotopic ossification started at birth up to 16 years of age, with a mean age of 4.6 years. In most cases of FOP the diagnosis has been long after the first symptoms of the disease, because it is a rare and little known disease. In this study, the median patient diagnosis was 9 years of age (Kaplan *et al*., 2008b; Dzukou *et al*., 2005). Of the 31 patients studied, three fathers were affected, one of the fathers had two sons with the disease and one another, two daughters, but only one daughter participated in the present study and the third father, a daughter. This condition is inherited in an autosomal dominant pattern and apparently with variable expressivity, which means that a copy of the altered gene in each cell is enough to cause the disorder. Although in most cases it is a new mutation (Connor & Evans, 1982; Dey, *et al*., 2016). Our findings regarding the first flare-up (Table 2) were similar to those observed in the literature, that is, predominantly located in the neck and back (Pignolo, *et al*., 2016). Progression of FOP will shortly limit patient walking, progressing to a wheelchair or even bedridden. Of the 31 patients studied, 19.34% had no complaints on walking, but around 48% of them already presented major difficulty and 9.68% already had limited walking limitations. In the evaluation of all of them, 7 (22.58%) are already wheelchairs dependent or are bedridden (Table 2). Because FOP is a rare disease and little knowledge about health procedures by professionals that may interfere with worsening of the prognosis, most patients end up having limitation of even the basic functions of food and hygiene and most of them over time, dependent on wheelchairs or bedridden at age 30 (Ortiz-Agapito & Colmenares-Bonilla, 2015). Almost 20% of the patients in this study have hearing problems, even a patient is already completely deaf. The hearing loss of patients with FOP has been reported in the literature and this loss is similar to those sounds in individuals with otosclerosis (Sorensen, 1987; Levy *et al*., 1999).

Regarding the temporomandibular joint, almost 40% of the patients already had some impairment of the opening of the mouth. Around 26% have 60% or more of difficulty opening their mouth. In the literature, there is little reference to the treatment of TMJ ankylosis (Herford & Boyne, 2003). In FOP, the temporomandibular joint involvement appears to be one of the most serious problems as a consequence of the disease, since the blocking of mouth movements leads to difficulty in feeding, allowing only the ingestion of food in the pasta or liquid form. Another difficulty is that of hygiene, because with the impossibility of hygienizing the occlusal and lingual portion of the teeth, it places patients with limitation in the opening of the mouth in a group at risk of oral diseases, such as caries and periodontal diseases. In addition, the lack of knowledge of the pathophysiology of the disease causes many dental professionals to refuse to give care to patients with FOP, causing great suffering of patients with dental pain and periodontal diseases. Another difficulty factor in the care of patients with blocked mouth is the access and lack of space for oral treatments, difficulty or even impossibility of performing the extraction of any dental element, especially posterior teeth. In general, even if the patient does not have a blocked mouth, the fact that there is contraindication to blockade anesthesia for treatment of lower teeth, this work for the dentist in the patient with FOP is very limiting. It has been reported that the permanent fusion of TMJ, predisposing to malnutrition, starvation and aspiration of food (Young, *et al*., 2007).

Because of the lack of knowledge of the consequences of trauma as a flare-up factor in FOP, many professionals report surgery for *hallux valgus* itself or even removal of heterotopic ossification, as well as other invasive procedures. In this study of the 31 patients, 11 patients underwent some procedure, referring to FOP or not, but the doctor who knows this disease will not even request a biopsy (Trigui, *et al*., 2011) much less, for example, the correction of the *hallux valgus* itself, by the knowledge of the consequences of the evolution of the disease. Some authors (Seok, *et al*., 2012) reported postoperative success without the appearance of ectopic ossification with the prescription of nonsteroidal anti-inflammatory drug (Naproxen). Of the patients in the study, 51.61% reported frequent cramps (Table 3), which is a symptom that has not

been reported in the literature. Cramps are sudden, involuntary, and painful muscle contractions. Its pathophysiology remains poorly understood. One hypothesis is that cramps result from changes in excitability of the motor neuron (central origin). Another hypothesis is that they result from spontaneous discharges of the motor nerves (peripheral origin). The hypothesis of central origin for experimental findings has been reported (Minetto, *et al*., 2017). FOP cramps may be due to poor circulation, compression of heterotopic bone or compression of nerves.

To date there is no effective treatment for FOP, and the most commonly prescribed treatment is the corticosteroid (Mohammad, *et al*., 2013; Sinha, *et al*., 2016), but others such as anti-inflammatory drugs , Palovarotene (Chakkalakal, *et al*., 2016)] and ascorbic acid (Palhares, *et al*., 2010) have also been reported. Of all patients in the study, 54.83% reported that they did not undergo any type of surgery. Four of them made corrections of *hallux valgus*, 4 others underwent biopsy. Seven others were submitted to different surgeries, not linked to FOP. Surgeries of valgus hallux and joints and ectopic ossifications can only induce new flare-ups and create new heterotopic ossifications (Pignolo, *et al*., 2013). The diagnosis of the majority of the 31 patients was exclusively clinical (8 cases), clinical suspicion and x-ray of the heterotopic ossifications (seven cases) and the others, by the associations of the exams, clinic, x-ray and DNA examination. But in knowing the characteristics of classical FOP, there is no need for molecular diagnosis. In some circumstances, the gene may have been inherited from the father or mother, as in the case of three fathers in this study (Table 3), who respectively had 2 sons with disease, other two daughters, but only one in this study and the third father, a daughter. The patient's phenotypes are dependent on the lifestyle of each one, depending on the aggressions suffered, especially the trauma due to falls and infections (Pignolo, *et al*., 2013).

Conclusions

The correlation of hallux valgus and FOP observed at birth by the physician in the delivery room and the knowledge of risk factors for disease progression, such as surgeries, intramuscular vaccines, dental treatments, may improve the prognosis of the disease in the long term.

Acknowledgement

This study is part of the Ph.D. thesis of MGP, with the support of the Graduate Program in Health and Development in the Central-West Region of MS, UFMS/Brazil. We appreciate greatly: Instituto de Assistência em Pesquisa, Educação e Saúde – IAPES, Campo Grande, MS, Brazil, by AWARD #: IAPES/2016-009.

REFERENCES

Ahn, J., Serrano de la Pena, L., Shore, E. M., Kaplan, F. S. 2003. Paresis of a bone morphogenetic protein-antagonist response in a genetic disorder of heterotopic skeletogenesis. *J Bone Joint Surg Am*., 85-A(4):667-74.

Chakkalakal, S. A., Uchibe, K., Convente, M. R., Zhang, D., Economides, A. N., Kaplan, F. S., *et al*. 2016. Palovarotene Inhibits Heterotopic ACVR1 (R206H) Fibrodysplasia Ossificans Progressiva (FOP) *Mutation. J Bone Miner Res*., 31(9):1666-75.

Cohen, R. B., Hahn, G.V., Tabas, J., Peeper, J., Levitz, C. L., Sando, A., *et al*. 1993. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. J Bone Joint Surg Am., 75:215–219.

Connor , J. M., Evans, D. A. 1982. Genetic aspects of fibrodysplasia ossificans progressiva. *J Med Genet.*, 19(1):35-9.

Dey, D., Bagarova, J., Hatsell, S. J., Armstrong, K. A., Huang, L., Ermann, J., *et al*. 2016. Two tissue-resident progenitor lineages drive distinct phenotypes of heterotopic ossification. *Sci Transl Med*., 23;8(366):366ra163.

Dzukou, T., Barbier, C., Spyckerelle, C., Labarriere, F., Vittu, G., Kremp, O. 2005. Fibrodysplasia ossificans progressiva in children. The interest of early diagnosis and treatment]. *Presse Med.***,** 12. 34(5):373-7.

Hasan, U. 2012. Fibrodysplasia ossificans progressiva without characteristic skeletal anomalies. Rheumatol Inter., 32: 1379–1382.

Herford, A. S., Boyne, P. J.2003. Ankylosis of the jaw in a patient with fibrodysplasia ossificans progressive. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*., 96:680-4.

Kaplan, F. S., Merrer, M. L., Glaser, D. L., Pignolo, R. J., Goldsby, R., Kitterman, J. A., *et al*. 2008a. Fibrodysplasia ossificans progressiva. *Best Pract Res Clin Rheumatol*., 22(1): 191–205.

Kaplan, F. S., Xu, M., Glaser, D. L., Collins, F., Connor, M., Kitterman, J., *et al*. 2008b. Early Diagnosis of Fibrodysplasia Ossificans Progressiva. *Pediatrics*. 121(5): e1295–e1300.

Kaplan, F. S.; Xu, M.; Seemann, P.; Connor, J.M.; Glaser, D. L.; Carroll, L.; Delai, P. *et al*.2009. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat., 9(30): 379–390.

Kaplan, F. S., Zasloff, M. A., Kitterman, J. A., Shore, E. M., Hong, C. C., Rocke, D. M. 2010. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am*., 92(3):686-91.

Kaplan, F. S., Shore, E. M., Glaser, D. L., Emerson, S., *et al*. 2013. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. *Clin Proc Intl Clin Consort FOP*. 1;2:1-72.

Levy, C. E., Lash, A.T., Janoff, H. B., Kaplan, F. S. 1999. Individuals with Fibrodysplasia Ossificans Progressiva. *American Journal of Audiology.*, 8: 29-33.

Minetto, M. A., Holobar, A., Botter, A., Farina, D. 2017. Origin and Development of Muscle Cramps. Medscape, February 26, 2017, http://www.medscape.com/viewarticle/777550.

Mohammad, A., Nermin, A., Sohier, Y., Amany, S., Bothina, H., Rasha, H. H., *et al*. 2013. Sporadic Fibrodysplasia Ossificans Progressiva in an Egyptian Infant with c.617G > A Mutation in ACVR1 Gene: A Case Report and Review of Literature. Case Reports in Genetics. 2013: 1-8.

Ortiz-Agapito, F., Colmenares-Bonilla, D. 2015. Quality of life of patients with fibrodysplasia ossificans progressiva. *J Child Orthop*., 9(6): 489–493.

Palhares, D. B. 1997. Myositis ossificans progressive. Calcif Tissue Int., 60; 4:394.

Palhares, D. B., Leme, L.M. 2001. Miosite ossificante progressiva: uma perspectiva no controle da doença. *J. Pediatr.*, 77;5:431-444.

Palhares, D. B., Leme, L. M., Naka, E. M., Melnikoc, P.2010. Fibrodysplasia Ossificans Progressiva: Oral Ascorbate and Intravenous Bisphosphonate during Flare-Ups. *J Muskuloskeletal. Pain*., 18;3:270-276.

Patin, G.1992. Lettres choises de feu M. Guy Patin. Letter of Aug. 27 1648 written to AF. Cologne: Laurens., 1:28.

Pignolo, B.J., Shore, E. M., Kaplan, F.S. 2013. Fibrodysplasia Ossificans Progressiva: Diagnosis, Management, and Therapeutic Horizons. *Pediatr Endocrinol Rev*. 10(0 2): 437–448.

Pignolo, R. J., Bedford-Gay, C., Liljesthröm, M., Durbin-Johnson, B.P., Shore, E. M., Rocke, D. M., *et al*. 2016. The Natural History of Flare-Ups in Fibrodysplasia Ossificans Progressiva (FOP): *A Comprehensive Global Assessment. J Bone Miner Res*.,31(3):650-6.

Seok, Y., Cho, S., Lee, E. 2012. Surgical treatment combined with NSAIDs in fibrodysplasia ossificans progressiva. *Ann Thorac Cardiovasc Surg.,* 18;1:61-3.

Singh, A., Pradhan, G. , Kumari, C., Kapoor, S. 2016. Early Recognition of Fibrodysplasia Ossificans Progressiva-Important For the Clinician. *JNMA J Nepal Med Assoc.,* 54(202):91-93.

Smith, R., Russell, R. G. G., Woods, C. G. 1976. Myositis ossificans progressiva: clinical features of eight patients and their response to treatment. J. *Bone Joint Surg*., 58: 48-57.

Sinha, S., Uchibe, K., Usami, Y., Pacifici, M., Iwamoto, M. 2016. Effectiveness and mode of action of a combination therapy for heterotopic ossification with a retinoid agonist and an anti-inflammatory agent. Bone. 90:59-68.

Shore, E. M., Xu, M., Feldman, G. J., Fenstermacher, D. A., Cho, T. J., Choi, I. H., *et al*. 2006. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet.,* 38(5):525–527.

Sorensen, M. S. 1987. Fibrodysplasia ossificans progressiva and hearing loss. *International Journal of Pediatric Otorhinolaryngology*., 14: 79-82.

Trigui, M., Ayadi, K., Zribi, M., Triki, Z., Keskes, H. 2011. Fibrodysplasia ossificans progressiva: diagnosis and surgical management. *Acta Orthop Belg*.,77(2):139-44.

Ulusoy, H. 2012. Fibrodysplasia ossificans progressiva without characteristic skeletal anomalies. *Rheumatol Int.,* 32(5):1379-82.

Weiss, T. C. 2010. Fibrodysplasia Ossificans Progressiva (FOP) - Facts and Information. Disabled World. http://www.disabled-world.com/disability/types/fop. Accessed 25 february 2014.

Young, J. M., Diecidue, R. J., Nussbaum, B. L. 2007. Oral management in a patient with fibrodysplasia ossificans progressiva. *Spec Care Dentist*., 27(3):101-4.

****