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Fibrodysplasia Ossificans Progressiva: treatment and oral considerations

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1. RESUMEN

La fibrodisplasia osificante progresiva (FOP) es una enfermedad rara que tiene una prevalencia mundial de uno de cada dos millones de individuos. La osificación heterotópica es la característica principal de esta enfermedad, donde tejidos no óseos son capaces de formar hueso de forma espontánea o provocada (golpes, infecciones, punciones intramusculares). En consecuencia, los pacientes afectados van progresivamente perdiendo movilidad y viéndose "atrapados" en un segundo esqueleto. La vida media de estos pacientes es de unos 40 años aproximadamente y, para evitar el rápido avance de la enfermedad, varias medidas se tienen que tomar en la vida diaria.

El objetivo de este trabajo es revisar la literatura en busca de información sobre la FOP, su tratamiento y, principalmente, las consideraciones orales en pacientes con esta enfermedad. Se redactan unas consideraciones en distintos enfoques de la odontología: alteraciones craneomandibulares, medicación, anestesia, odontología conservadora, cirugía y ortodoncia. La información obtenida está basada principalmente, en casos clínicos aislados o series de casos clínicos.

A pesar de las limitaciones en la cantidad de información disponible, la conclusión es que el tratamiento y manejo dental de estos pacientes tiene que estar en manos de un equipo multidisciplinar y entrenado. La principal complicación a nivel oral en estos pacientes es la anquilosis de la articulación temporomandibular (ATM) que conlleva a problemas de nutrición y un difícil acceso a la cavidad oral. La función del odontólogo es la de mejorar la calidad de vida de estos pacientes siempre evitando acciones que empeoren su situación y provoquen un episodio de osificación. Estarían totalmente contraindicada la técnica de anestesia troncular y los procedimientos que requieran un estiramiento excesivo de la ATM. Sin embargo, no hay suficiente evidencia científica y más estudios sobre el manejo odontológico deben realizarse en estos pacientes.

2. ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare disease with a worldwide prevalence of one in two million individuals. Heterotopic ossification is the main characteristic of this disease, where non-osseous tissues are able to form bone spontaneously or caused (blows, infections, intramuscular punctures). Consequently, affected patients progressively lose mobility and see themselves "trapped" in a second skeleton. The average life of these patients is about 40 years and, to avoid the rapid progression of the disease, several measures have to be taken in daily life.

The objective of this work is to review the literature in search of information about FOP, its treatment and, mainly, oral considerations in patients with this disease. Some considerations are drawn up in different approaches in dentistry: craniomandibular alterations, medication, anesthesia, conservative dentistry, surgery and orthodontics. The information obtained is mainly based on isolated clinical cases or series of clinical cases.

In spite of the limited information available, the conclusion is that treatment and dental management of these patients have to be approached by a multidisciplinary and trained team. The main oral complication in these patients is ankylosis of the temporomandibular joint (TMJ) that leads to nutrition problems and difficult access to the oral cavity. The function of the dentist is to improve the life quality of these patients by always avoiding actions that worsen their situation and cause an episode of ossification. The technique of truncal anesthesia and procedures that require excessive stretching of the TMJ are totally contraindicated. However, there is not enough scientific evidence, and more studies of dental management should be performed on these patients.

3. INTRODUCTION

Heterotopic ossification (HO) or heterotopic bone formation, is the presence of bone where bone normally does not exist, that is, non-osseous soft tissues. This disorder can be confused with different types of calcification such as metastatic calcification and dystrophic calcification- that can be found in several types of tumours- (1).

Existing evidence states that the formation of ectopic bone in vivo requires three base conditions: a cell capable of osteogenic differentiation, the presence of inductive agents and a permissive local environment (2).

There are two types of HO, the acquired form and the hereditary form. In the acquired form, HO usually is precipitated by trauma (such as fracture, total hip arthroplasty, or direct muscular trauma) or has a neurogenic etiology (such as spinal cord injury or central nervous system injury) (1). In the hereditary form, heterotopic ossification is a common feature of at least three distinct genetic disorders that affect humans: fibrodysplasia ossificans progressiva (FOP), Albright's hereditary osteodystrophy, and progressive osseous heteroplasia (3).

To give an accurate diagnosis of this conditions clinicians request bone scanning and other imaging studies for patients at risk of HO. In conventional radiographies, the typical appearance of HO is circumferential ossification with a lucent centre (1).

Although the different types of HO have been recognized and classified, complete knowledge of the etiology and successful prevention and treatment remain difficult to define. In these patients it can be observed symptoms such as fever, swelling, erythema and decreased joint motion, which create problems to clinicians to treat and diagnosticate HO. This because they can mimic the presentation of other pathologies such as cellulitis, osteomyelitis, or thrombophlebitis (1).

In oral and maxillofacial region, it could be found different types of HO. In the acquired form it has been described cases of muscular ossification induced by trauma, ankyloses of temporomandibular joint, ossification of styloid complex -Eagle Syndrome-, and so on.

In this review it will be approached all aspects of fibrodysplasia ossificans progressiva (FOP), its clinical and radiographic features, treatment and medical concerns. In order to establish oral consideration for dentist to treat these patients.

3.1 FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

This condition is very rare and disabling. Its worldwide prevalence is approximately one in two million individuals, and there is no ethnic, racial, gender, or geographic predisposition (4). In Spain in 2012 a total of 24 individuals were identified as FOP cases (5).

Most of sporadic and familial cases of classic Fibrodysplasia Ossificans Progressiva (FOP) have a mutation in activin receptor IA/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor. ACVR1 is expressed in numerous tissues of the body, including skeletal muscle and cartilage. Its function is to control the growth and development of bones and muscles, including gradual replacement of cartilage by bone through endochondral ossification (6).

The classical mutation present in most cases of FOP is the single nucleotide change in ACVR1 (c.617G>A, p.R206H), which results in altering Arginine at position 206 to a Histidine (7,8). This mutation has been reported in 200 cases worldwide by the time Hüning et al. (8) did their research (2014). This amino acid substitution results in a conformational change of the receptor that alters its ligand-binding properties and activity. Besides this classic mutation, other ACVR1 mutations were found in literature in 14 patients, representing 10% of FOP cases worldwide. There is a common molecular mechanism that is shared between the different mutation's type, although is unknown nowadays. There is some phenotypic variation in "non-classic" FOP cases, which will be described in "clinical characteristic's" paragraph (7,8).

The discovery of the FOP gene in 2006 by Shore et al., (9) enabled to make steps ahead through the understanding of FOP and to get a therapeutic target in the BMP signalling pathway and so an effective treatment.

CLINICAL CHARACTERISTICS

FOP is characterized by congenital malformations of the great toes (Figure 1) and progressive heterotopic endochondral ossification (HEO). This great toe malformation can vary from a fibular deviation or their complete absence (8).

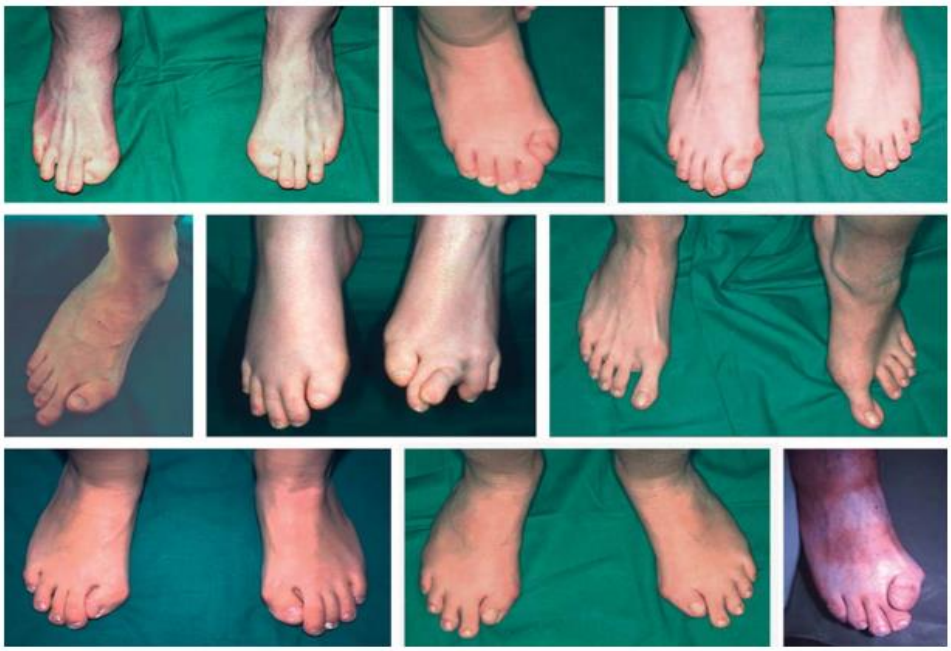

Figure 1. Congenital malformation of the great toes (brachydactyly and fibular deviation).

Source: Hüning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. Mol Syndromol. 2014; 5(5):201–11.

Flare-ups are swellings that begin to occur mostly in childhood of patients with FOP, these swellings can regress with no complication but most of them are the previous step for HEO, transforming soft tissue in mature heterotopic bone. Flare-ups can appear without any cause or can be promoted by a minor trauma such as: vaccinations, mandibular blocks, muscle fatigue, bruises, falls, or viral illnesses. Typical features of FOP flare-ups usually are intense muscle edema, fibroproliferation, and angiogenesis. The lesions propagate rapidly into adjacent tissue, it may appear within hours and can reach an alarming size in less than a day (10).

Anatomically heterotopic ossification is commonly first seen in the dorsal, axial, cranial, and proximal regions of the body and later seen in the ventral, appendicular, caudal, and distal regions. Several tissues of the body are exempt of ossification: skeletal muscle such as diaphragm, tongue, and extra-ocular muscles. Also, cardiac and smooth muscle are spared from HEO (10).

In addition to classic features of FOP, some patients have other abnormalities such as cervical spine with large posterior elements, tall and narrow vertebral bodies, and fusion of the facet joints between C2 and C7. Other skeletal malformations associated with FOP are short thumbs, clinodactyly, short broad femoral necks, and proximal medial tibial osteochondromas (8).

Proximal tibial osteochondromas have been described as a feature associated with fibrodysplasia ossificans progressiva. Osteochondromas are benign orthotopic osteocartilaginous lesions composed of cortical and trabecular bone with an overlying hyaline cartilage cap. Deirmengian et al. did a research over ninety-six patients with FOP, concluding that tibial osteochondromas has to be considered a common phenotypic feature present in up to 90% of FOP cases (11).

It is also important to highlight not only the clinical features but also the classical complications caused by the HEO. Main complications described in FOP patients are: hearing loss, temporomandibular joint ossification and thoracic insufficiency syndrome.

Hearing loss is a typical complication in FOP patients. Usually is driven by middle ear ossification but can also be present in patients with sensorineural hearing impairment- involving inner ear, cochlea o auditory nerve. The type of loss is predominantly conductive in nature, similar to that seen in individuals who have otosclerosis (8).

Joint ossification in FOP patients start within the first decade of life**. Temporomandibular joint (TMJ)** is not exempt of this ossification which leads to an immobility and inability to open the mouth. Over-stretching of jaws, mandibular blocks and surgical trauma for heterotopic bone excision can accelerate the ossification of TMJ (12).

Thoracic insufficiency syndrome (TIS) appears due to a limited chest expansion, usually in moderate stage of the disease. In advanced stages of the disease this TIS is characterized by a rigid chest wall without expansion and exclusively diaphragmatic breathing (13).

As well as FOP is a rare disease, there is not enough awareness of it and is commonly misdiagnosed with different pathologies such as aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma. The main mistake is not to associate the episodes of flare-ups with the malformed great toes (10).

The misdiagnosis of FOP approaches 90 per cent of all cases worldwide (14). This is a great percentage of misdiagnosis, which leads to unnecessary and harmful diagnostic biopsies that exacerbate the progression of the condition. Lesion's biopsies can be dangerous at any anatomic site, but especially so in the neck, back, and jaw where HEO can lead to rapidly progressive spinal deformity, exacerbation of thoracic insufficiency syndrome, or ankylosis of the temporomandibular joints (10).

FOP cannot be diagnosed prenatally (15). The correct diagnosis of FOP is not difficult to carry out, it can be found out clinically just associating the flare-ups episodes or the soft tissue lesions with symmetrical malformations of the great toes. This can be made even before radiographic evidence of HEO.

In addition to clinical manifestations, imaging analysis is a key aspect in the diagnosis. Conventional radiographies cannot detect initial stages of HO, instead computed tomography scan (CT) clearly reveals typical HO. Moreover, magnetic resonance imaging (MRI) is also an important tool for diagnosis of FOP and it can reveal pre-osseous lesions, usually appearing as soft tissue swelling (15). The most reliable and definitive diagnosis is made by the detection of the ACVR1/ALK2 gene. The early gene detection allows to give an accurate diagnosis of FOP even before the HEO appear, reducing the trauma caused by unnecessary biopsies and avoiding all factors that trigger ossification. In addition, this gene detection it also helps to identify other rare diseases like FOP (15).

PROGNOSIS

As we have exposed, FOP disease is devastating and has several complications that threatens life. Its prognosis is so poor, there is no specific treatment available and a low prevalence which make it a rare disease.

Heterotopic ossification usually begins by ten years of age, involving firstly neck and shoulder (16). These ossifications lead to a significant limitation of osteo-articular mobility, principally ossification of the hip, knee, shoulder and elbow (Figure 2). When this inability to move get worse, is called the stage of “stone man” reported in only about 600 patients (3). At this advanced stage, the patient usually develop pressure ulcers secondary to TIS and immobility (3). The median lifespan expectancy is 40 years and death results most commonly from complications of thoracic insufficiency syndrome or pneumonia (16).

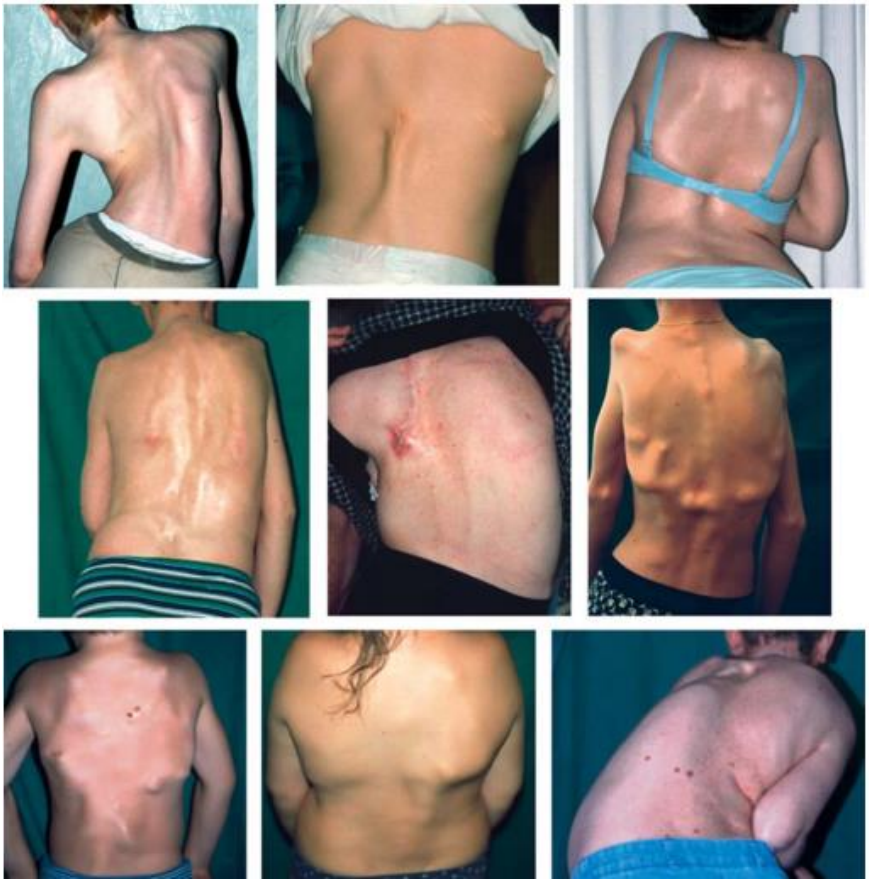

Figure 2. Patients with the 'classic' mutation c.617G>A (p. R206H) in the ACVR1 gene. In the typical course of disease, patients develop severe scoliosis and thorax insufficiency

Source: Hüning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. Mol Syndromol. 2014; 5(5):201–11.

Nowadays the challenge in FOP community is to get awareness of the disease for clinicians in order to prevent misdiagnosis and to get a specific cure. Several studies about pharmacological specific treatment are being carried out to finally get a cure, increase the median lifespan in patients with FOP, and to add life quality.

In dentistry it would be a great step forward to set clinical guidelines to treat these patients in order to prevent worsening patient's clinical conditions while treating by safe techniques. As already seen in previous parts of this review, the disease has a low prevalence, which, jointly with few high evidence studies create the need to provide to dentists a clinical protocol to, and so, here comes the attempt to provide it.

4. OBJECTIVES

The aim of this review is to describe fibrodysplasia ossificans progressiva, searching in literature information about heterotopic ossification in the oral and maxillofacial region. Furthermore, it has been attempted to set clinical considerations for dentist and clinicians to treat these patients.

5. DESIGN

This study was draw up as a **literature review**, in order to synthesize all the scientific information available to allow the professional to acquire and update knowledge about patients with FOP and its management.

6. MATERIAL AND METHODS

This review has been written as the Final Degree Thesis of Dentistry degree in the University of Barcelona in 2017/2018 course year.

Search strategy

Electronic search was performed by one reviewer from December 2017 to March 2018. The Internet databases selected were the national Library of Medicine, (MEDLINE, PubMed) and the Cochrane central register of clinical trials. In addition, this search was enriched by hand-searches, citation screening, expert recommendations and all reference lists were scanned for possible additional studies.

There has been a collaboration between the reviewer and the Spanish association of Fibrodysplasia Ossificans Progressiva *("Asociacion Española de Fibrodisplasia Osificante Progresiva- AEFOP*"), which provided an important number of articles and information about the disease. In addition, the specialist of FOP in Spain, Doctor Javier Bachiller got in touch with the reviewer to help with oral considerations and provided his lasts research works.

The key search words used in PUBMED database are exposed on this chart:

Key word	**Articles number**
Heterotopic ossification AND buccal	8 articles
Fibrodysplasia ossificans progressiva AND dental NOT hip last 10 years	33 articles
Fibrodysplasia ossificans progressiva NOT hip NOT elbow last 5 years only reviews, meta-analysis and systematic reviews	60 articles

All studies selected were identified and screened by the reviewer to achieve the maximum evidence available.

Inclusion criteria

For this study several criteria were established to assess adequate information:

- Studies written in English and Spanish were included.
- The data of publication wasn't limited to get the maximum available evidence.
- Articles related to heterotopic ossification in oral and maxillofacial region.
- Cases reports, Clinical trials, Comparative studies, Systematic reviews and Meta-analysis.

Exclusion criteria

- Ossification associated to tumours.
- Articles related to ossification not in the oral or maxillofacial region, such as hip or elbow ossification.

Risk of bias assessment

The quality of the selected studies was evaluated by the reviewer, following parameters as, a clear definition of inclusion and exclusion criteria, clear definition of the pathologies and correct literature research in cases reports.

7. RESULTS

Results of literature search are now exposed in two different paragraphs: treatment and oral consideration. Both paragraphs are different not only in content but also on search strategy. On the one hand, pharmacological treatment paragraph is redacted with a general view of available options to treat FOP patients and, also, investigation approaches for future specific treatment. On the other hand, oral considerations search was more difficult and, moreover it is considered the focus of this review. Most of the information was extracted from clinical cases in order to get the maximum evidence available.

7.1 TREATMENT

There is still no successful treatment for FOP, prevention is the best weapon to slow down the progression of this condition, along with pharmacologic symptom support. Some measures must be carried out on a daily basis such as: household safety improvements, utilization of ambulatory devices, and body protection to prevent falls and minimize injuries (6).

As there are no enough evidences about pharmacological treatment in patients with FOP, several options are available for clinicians to treat flare-ups symptoms:

a. **Corticoids** are most used drugs, its potent anti-inflammatory effects make appropriate to use it early in the course of a FOP flare-up (10). Anecdotal reports from the FOP community suggest that a brief 4-day course of high-dose corticosteroids - begun within the first 24 hours of a flare-up - may help reduce the intense inflammation and tissue edema seen in the early stages of the disease (10).
b. Other drugs used in FOP patients are **mast cell inhibitors**, this is because, as said before, flare-ups appears suddenly and spreads rapidly, this suggests involvement of inflammatory mediators along with an abnormal connective tissue wound response, and indicates that there is a potential role of inflammatory mast cells and their mediators in the extension of the disease process (10). Brennan et al., demonstrated that Cromolyn (mast cell inhibitor drug) is very safe and effective in abrogating HO in an injury-induced mouse model of FOP (17).
c. Another medication group that have also an important implication in FOP are **selective cyclo-oxygenase-2 (cox-2) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs).** This because, inflammatory prostaglandins are potent co-stimulatory molecules along with BMPs in the induction of heterotopic ossification. In addition to their potent anti-

inflammatory effect, they have potent anti-angiogenic properties at high dosages, a characteristic that makes them even more suitable for their use in FOP.

d. **Bisphosphonates** are another potent class of medications that have profound effects on bone remodelling and exert their primary effect by decreasing the life span of osteoclasts. Several studies demonstrated the effectiveness of bisphosphonates to prevent HO in flare-ups episodes (18). However, recent studies affirm that bisphosphonates do not affect heterotopic ossification enhanced, and they suggests that osteoclasts are not important targets in the treatment of heterotopic ossification in FOP (19). This is the reason why they are not used routinely for FOP, furthermore they are commonly used along with corticoids.

To sum up, Pignolo et al. (20) presented key considerations for treatment in FOP patients depending on the anatomically situation of flare-ups. (Figure 3)

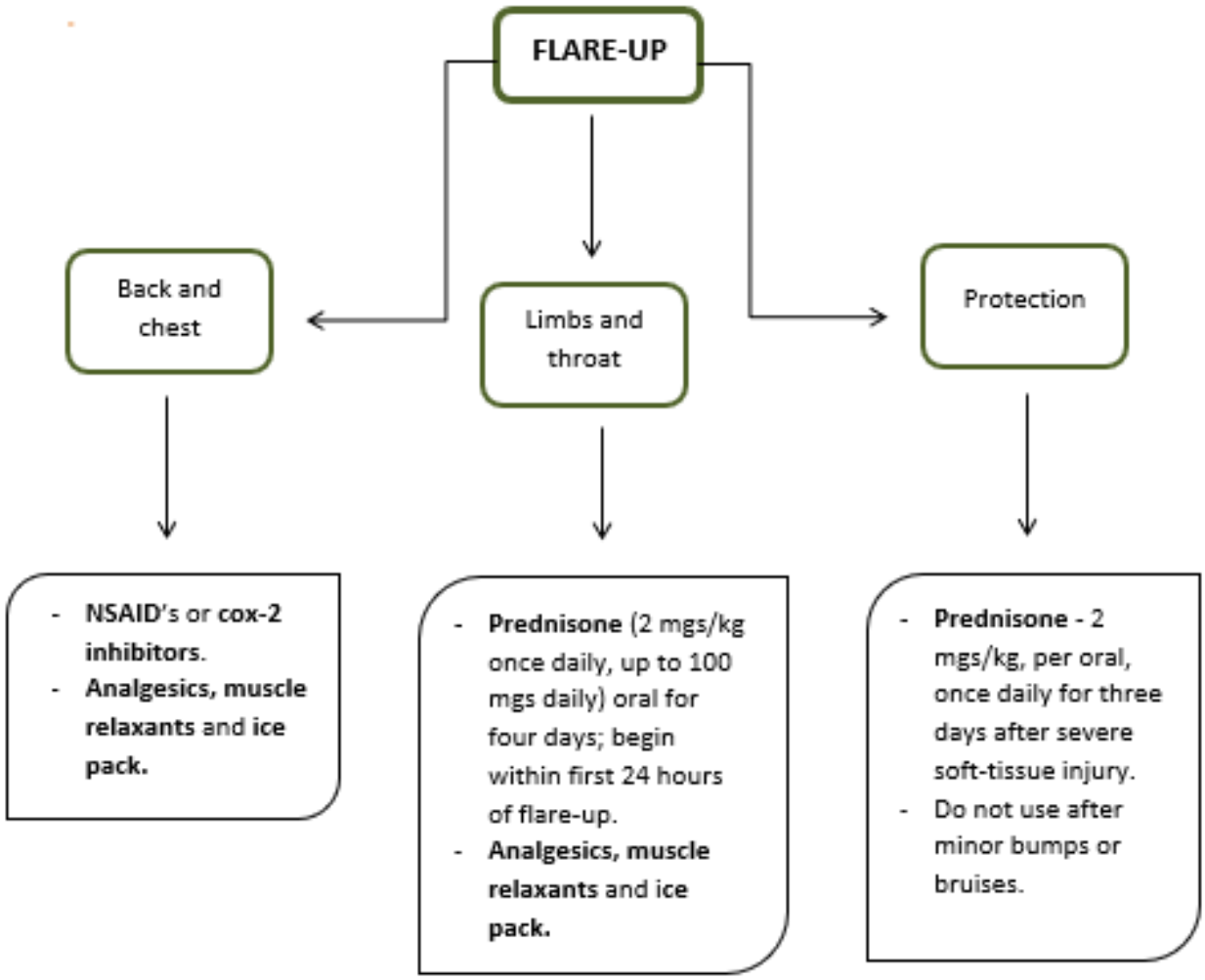

Figure 3. Diagram of treatment according to Pignolo et al. (2013)

Despite all this pharmacological option, their target is only to treat flare-up symptoms. Nowadays, the researcher's efforts are to development a treatment that will prevent, halt or reverse the progression of FOP (10). The discovery of the FOP gene and all the research done about heterotopic ossification in FOP patients reveals at least four long-term approaches to the treatment and/or prevention of FOP (20):

1) Blocking Activity of the Mutant FOP Receptor

Dorsomorphin is a signal transduction inhibitors (STIs), a kind of molecule that have the potential for development into powerful therapeutic agents. This molecule inhibits all type I BMP receptors (ALK2, ALK3, and ALK6). The goal is to specifically block ALK2, for this reason the treatment must have specificity, efficacy, and tolerance to resistance, acceptable safety profiles, and lack rebound effect before they can be tested in clinical trials for FOP (20).

2) Deviating mesenchymal stem cells (MSCs) and chondroprogenitor cells from an osseous to a soft tissue transformation

Shimono et al. demonstrated that **retinoic acid** is a potent skeletal teratogen that inhibits chondrogenesis. This is because modifies a specific pathological process of tissue metamorphosis that requires the BMP signalling pathway (20). Palovarotene is a highly selective retinoic acid receptor gamma (RAR-γ) agonist, Wheatley et al. did a recent study in animal model where the results indicate that Palovarotene inhibits traumatic HO formation (21).

3) Inhibiting the Inflammatory and Neuro-inflammatory Triggers of FOP Flare-ups

In FOP sensory nerves regulate the innate immune system and amplify the formation of heterotopic bone. Several studies are being carried out about **substance P**, an 11 amino acid neurotransmitter, and potent neuroinflammatory protein that plays a key role in heterotopic ossification (22).

4) Inhibiting the Mutant FOP Allele

Kaplan et al. generated an allele-specific siRNA (ASP-RNAi) duplexes, which are a powerful tool to silence gene expression. Their results provide proof of principle that ASP-RNAi has potential therapeutic efficacy for the treatment of FOP but more studies have to be done in animal models (23).

7.2 ORAL CONSIDERATIONS

FOP patients have same dental problems as the general population, they can suffer several oral pathologies such as: caries, periodontal disease, malocclusion, impacted teeth, and so on (12).

In this work, several oral considerations are attempting to describe different approaches in dentistry: craniofacial alteration, medication, preventive dentistry, anesthesia, restorative dentistry, surgery and orthodontics.

A. Craniofacial alteration- TMJ ankylosis

FOP patients usually have mandibular hypoplasia which cause retrognathia and maxillary overbite. Carvalho et al. (24) provided a study in 2011 where seven patients diagnosed with FOP were evaluated retrospectively. CT evaluation revealed in three patients HO involving the pterygoid muscles with elongation of the lateral pterygoid plate that extended to the mandibular ramus (Figure 4). These patients had significant history of trauma or surgery in midface, so this reflects the importance of the caution that has to be taken in oral handline, even though it is known that HO can appear without any concrete cause (24).

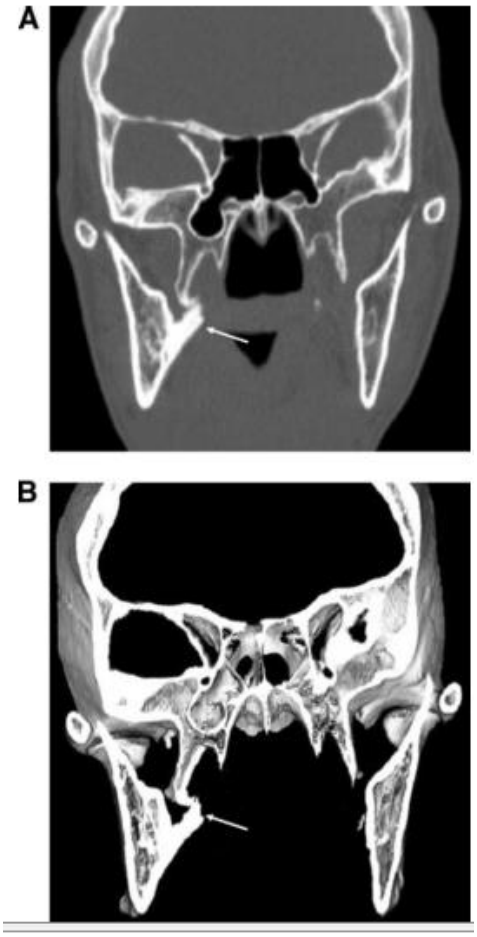

Figure 4. A Coronal orthogonal reformatting showing growth of the lateral pterygoid plate, heterotopic ossification of the right pterygoid muscles, and ankylosis of the mandibular ramus and lateral pterygoid plate (arrow). **B**, Volume rendering revealing hypertrophy of the left lateral pterygoid plate and ankylosis with the mandibular ramus (arrow).

Source: Carvalho DR, Farage L, Alves BJ, Martins F, Speck-Martins CE. Craniofacial findings in fibrodysplasia ossificans progressiva: computerized tomography evaluation. YMOE. 2011; 111:499–502.

All of the patients in this case series (24) had ossification of the stylohyoid ligament, and they did not have pain that is characteristic of Eagle syndrome.

Extra-articular ankylosis of the TMJ is a major complication in FOP patients as we exposed previously, it can cause mouth aperture limitation with alimentary problems and severe weight loss (24). This condition is less frequent in younger patients (24).

B. Medication

It is important to assess patients in an integral mode. When a patient is in our box all medical conditions and medication have to be considered. FOP patients could take several drugs as we exposed in previous paragraphs. There is not a definitive treatment plan for all cases of FOP, so every patient has a personal approach made by the specialist clinician. In addition, FOP patients not only have FOP medication but can also have different conditions such as: diabetes, hypertension, and so on. All drugs that patients take to prevent, or control disease expose them to the risk of developing adverse reactions.

Xerostomia is the most common drug reaction that affects oral cavity. Taking one or more drugs makes two times more probable to develop xerostomia than taking any medication. This complication is associated with over 500 drugs, including non-steroid anti-inflammatory drugs (NSAIDs). Complications of xerostomia are taste alternations, dysphagia, speech disturbance, dental caries and susceptibility to infections (25).

Other complications that have to be considered is **osteonecrosis**, a serious oral complication from taking bisphosphonates (BPs), anti-resorptive (denosumab), anti-angiogenic, and immunomodulatory medication. This complication results from temporary or permanent loss of blood supply to the bone.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is more common in patients with cancers treated with intravenous BPs, and it is uncommon in patients on oral administration (0.1- 0.4% in orally taking versus 0.8- 12% in IV injection) (25). Most commonly, tooth extraction is the initiator factor. Although patients with FOP are not in the group of high risk, and there is no published case of BRONJ in FOP patient, the dentist has to consider the risk in patients taking long period bisphosphonates (25).

C. Preventive dentistry

Prevention is the most important part of oral treatment in all patients, but in those with FOP is essential to avoid any kind of intervention that could lead to a deterioration of the condition.

The clinician has to strive to give accurate oral hygiene instructions and to follow a control in these patients. Hygiene and caries control are the basis of preventive dentistry, avoiding extended procedures and manipulation of oral soft tissues (26). In patients with ankylosed temporomandibular joints (TMJs), regular hygiene instruction is not enough. In addition, professional instrumentation and special toothbrushes may be helpful, although its use is often limited to the buccal surfaces (27).

Other measures have to be taken in patients with limitation of mouth opening and limitation of movement, such as chlorhexidine rinses and topical and fluoride supplementation. This is in addition to regular prophylactic care, and allows to reach lingual surfaces of teeth (26).

Fluoride varnish is an effective tool for arresting the progression of enamel carious lesions in primary and permanent teeth. Fluoride is accumulated on bacterial plaque and saliva as calcium fluoride, in active incipient carious lesions the acidic environment reacts with the enamel surface by stimulating available calcium fluoride dissolution to inhibit the demineralization and enhance the remineralization (28).

D. Anesthesia

If the preventive phase fail, several pathologies can appear in the patient, such as caries or periodontal disease. Most of oral treatments need anesthesia to carry out the procedure with no pain. Pain control is as important in this population as in any other, but several considerations need to be kept in mind. As already exposed, patients with FOP cannot receive intramuscular puncture, which make mandibular block anesthesia forbidden. If they have block anesthesia, they may set up a reaction that will ankylose the jaw, with all the catastrophic consequences exposed previously. In those cases where local anesthesia is not possible, the best choice is general anesthesia (Figure 5).

When general anesthesia is needed, the approach has to be multidisciplinary. General anesthesia offers an excellent pain control that avoid the use of local anesthesia excepting in cases where haemostasis control is needed. The difficult part of these cases is successful intubation and usually an awake fiberoptic intubation is the best option. A skilled anesthesiologist has to pass a breathing

tube fiberoptically into the trachea, so the patient can breathe spontaneously and control his secretions until general anesthesia is done (12).

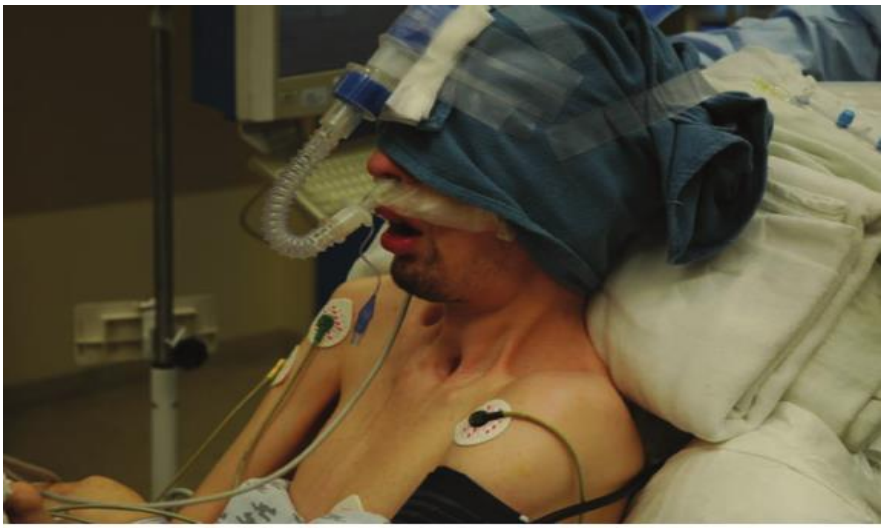

Figure 5. Patient with complete fusion of the bones in the neck.

Source: Wadenya, R. et al. A description of two surgical and anesthetic management techniques used for a patient with fibrodysplasia ossificans progressiva

Luchetti et al. (1996), did a research in FOP community, where a survey established that injections of local anesthetic during dental procedures are substantial added risk for inciting heterotopic ossification in patients with FOP (29). Twenty-one of the thirty-six patients who had dental work performed had received an injection of a local anesthetic during the procedure, five patients reported an immediate FOP flare within several days of an injection and only one of the twelve patients who had fillings or extractions performed without injections had developed heterotopic ossification as a result of the procedure. Even though, this research is probably the most significant in oral field and FOP community, it has several biases. On one hand, it is based on the records and memories of patients and their families rather than on clinician-generated dental records. On the other hand, it is not described whether the injections occurred in the maxilla or in the mandible or whether they were infiltrations or nerve blocks (29).

To conclude, in dentistry the injection of a local anesthetic should be avoided whenever possible. If pain control is needed, injections should be as atraumatic as possible, and should be limited to subcutaneous infiltration (29).

E. Restorative dentistry

Classical restorative dentistry becomes a challenge in patients with limited access to the oral cavity, where non-traditional approaches are necessary to caries removal and restoration (12). In patients with jaw ankylose or patients with insufficient interocclusal opening, access to caries may be made through a buccal approach instead of through the occlusal, in order to do it some tools are available to retract tissues such as: malleable ophthalmic and neurosurgery retractors (26).

Figure 6. A: Ribbon Retractor, malleable. **B**: Desmarres Lid Retractor. Ophthalmologic retractor.

To gain access to occlusal fissures, a small round burr on a slow speed handpiece can be used from buccal approach. Also, pediatric instruments such as short shank burrs should be used. For inter-proximal cavity preparations, metal matrix strips can be placed between the teeth and wedged into place (12).

Best filling material in cavities that are difficult to reach are flowable dental materials, and also, for patients with poor oral hygiene, reduced salivary flow, or inability to gain complete access to the teeth, glass ionomer restorative materials offer fluoride release and protection, as we said in preventive paragraph (12).

F. Oral surgery

There are several reasons why dentist could carry out a tooth extraction in FOP patients. Some indications could be: teeth severely damaged by caries with no possible restoration, roots tissue damage (rhizolysis), teeth truly damaged by periodontal disease, in teeth with an extensive

periapical infection, teeth damaged by trauma or even to ease nutrition in patients with total ankylose of TMJ.

Oral surgery is a challenge when there is a limited mouth opening. In the posterior dentition, usually there is not enough space for forceps and a buccal approach has to be made to gain access to the teeth to be extracted (12).

The adequate extraction technique includes odontosection and exposition of root by ostectomy. An incision along the alveolar crest has to be made to reflect the tissue, with a burr buccal bone is removed, exposing the roots. The tooth is then sectioned and the clinical crown is removed from the buccal space, with individual root elevation (12).

On the other hand, it is known that permanent fusion of the TMJ leads to malnutrition, inanition, and risk of aspiration of food or vomit. Management of inanition associated with limited mouth opening in patients with FOP is important due to its complications and requires a multidisciplinary approach that includes a nutritionist or dietitian who supervise diet (26).

According to Young et al., selective extractions - mainly first molars - create enough space in patients with TMJ permanent fusion to restore oral diet. The interocclusal space created by extraction of molars can augment nutritional improvement (26).

Condylar osteotomies have been described to gain access to the oral cavity, restorations, and/or extraction of damaged teeth. However, all surgical procedures including bilateral subcondylar osteotomies are best avoided as these have been universally unsuccessful, leading to recurrence with increased disability (27).

G. Malocclusion and orthodontics

According to Nussbaum et al., there is high incidence of mandibular hypoplasia and large overjet in patients with FOP, resulting in an Angle Class II Division 1 occlusion. This malocclusion seems to be helpful for cleaning the oral cavity and for eating in patients with TMJ ankylosis. (30)

Luchetti et al., did a research in FOP community about dental care, six of the 21 patients had used orthodontic appliances, and none of the six patients reported FOP flare-ups as a result of that therapy. This suggest that orthodontic care could be safe in FOP patients, but always watching to avoid overstretching of the jaw in any dental procedure (29).

To sum up, maxillary protrusion seems to be common in patients with FOP and orthodontic treatment would be safe. However, space for cleaning the mouth and eating needs to be taken into consideration (31).

8. DISCUSSION

Redacting this review, several inconvenient were overcome. In first place, there is a lack of information in scientific literature about specific treatment and oral consideration in FOP patients. On the other hand, there is also a lack of evidence in the article available in literature. So finally, there are only a few studies available in the literature and they are low-evidence based.

The search was carried out not only in scientific databases, but also specialist recommendation was considered, mainly from the Spanish Association of FOP (AEFOP). FOP community is very aware of the importance of scientific investigation to push forward knowledge about management of the disease.

Regarding pharmacological treatment, it is observed in results that the only available treatment is mainly symptomatic, including NSAID, corticoids, and selective inhibitor of cyclo-oxygenase-2 (cox-2). Nowadays, more specific treatments are in investigation phases, with hope that could be effective to treat this disabling disease.

Regarding oral consideration, results are based mainly in clinical cases and some study, such as the one did by Luchetti et al. in 1996 (29), made by an email survey. All of this leads to a result based on small samples with evident bias to stablish general consideration based in scientific evidence.

The real challenges in FOP patient's oral management are:

1) Avoiding any action that could lead to an ossification.
2) Patients with limitation of mouth opening.
3) Consider medication for interactions or contraindication of procedures

To achieve this, the most important is to have information about this disease and its management. In addition, a multidisciplinary team and a hospital environment are necessary, in many cases. As we observed in most clinical cases, to achieve pain management, general anesthesia is the best option, and this leads to the need for a team trained in the care of patients with FOP.

Regarding the management of oral pathologies, the most important is to insist on oral hygiene instructions and preventive dentistry. In some cases, as is discussed in the results, additional measures are necessary such as chlorhexidine or fluoride rinse, special small toothbrushes and periodic professional tartrectomies.

All the techniques performed in the oral cavity will be modified in cases of opening limitation. It is necessary to perform access manoeuvres for any type of procedure, both for caries restorations and for extractions; that allows us to do our work avoiding overstretching of the jaw.

On the other hand, it is known that orthodontic treatments could be safe for patients with FOP, since there are cases described of orthodontic patients without episodes of flare-ups (29). This is due to the low invasiveness of these treatments, they do not require most of the time anesthesia and, in addition, tooth movements are performed very slowly. However, orthodontic treatment is not fully justified for aligning teeth in an Angle class I, since they are patients who will most often lose the interocclusal space due to ATM ankylosis and will need a way to eat, which can include extractions of posterior pieces, as described by Young et al. (26). For this reason, the use of orthodontic techniques in a patient with FOP is somewhat controversial and there is no clear answer to the best option.

There are types of treatments that are not described in scientific literature such as: scaling, root planing and periodontal treatment, endodontics and the use of prostheses in patients with FOP. The conservative trend in dentistry is a little doubtful in patients with FOP and it is probably preferable to perform an extraction than an endodontics in patients with a tooth with extensive caries that affects the pulp. However, there could be cases of exception, such as: very young patients or teeth with easy access to perform endodontics.

The treatment of scaling and root planing would be justified in patients with periodontal disease and accumulation of subgingival calculus, however, there is no scientific evidence to support the safety of this type of treatment.

Regarding the lack of information on prosthetic rehabilitation in patients with FOP, it is known that the life expectancy in these patients is approximately 40 years, an age in which the loss of teeth does not prevail. In addition, TMJ ankylosis problems, cause the need to have an interocclusal space in order to have a correct nutrition, as already mentioned above. Therefore, the option of prosthetic rehabilitation could only apply in very extreme and special cases of tooth loss at an early age due to trauma, for example. So far there is no case described of this type.

9. CONCLUSIONES

1. La fibrodisplasia osificante progresiva es una enfermedad rara, con una baja prevalencia que tiene un curso discapacitante para el paciente. Los episodios de osificación heterotópica pueden estar provocados o pueden aparecer sin ningún factor precipitante.
2. El tratamiento disponible actualmente es, principalmente, sintomático. Tratamientos más específicos están en fases de investigación.
3. A nivel oral los pacientes con FOP tienen la misma prevalencia de patologías orales que la población general. La complicación más prevalente es la anquilosis de la ATM con limitación de apertura bucal. Esto provoca problemas de nutrición por incapacidad de alimentarse y además limitación de acceso a la cavidad bucal para las medidas de higiene por parte del paciente.
4. El tratamiento odontológico en estos pacientes requiere, en muchas ocasiones, un equipo multidisciplinar y entrenado. El control del dolor mediante anestesia local puede no ser siempre posible de lograr, la anestesia troncular es una técnica prohibida por riesgo de osificación tras punción muscular. En estos casos, la anestesia general es la mejor opción.
5. Es importante evitar el estiramiento excesivo de la ATM, por lo que es necesario realizar modificaciones de las maniobras de acceso tanto para caries como para exodoncias o cualquier tipo de tratamiento, donde en muchas ocasiones el único acceso es de la cara vestibular.
6. Hay una falta importante de estudios científicos sobre el manejo oral de pacientes con FOP, y muy pocos casos descritos en la literatura. Mas trabajos de investigación deberían realizarse para lograr establecer un protocolo clínico de actuación para odontólogos en estos pacientes.

10. CONCLUSIONS

1. Fibrodysplasia Ossificans Progressiva is a rare disease, with a low prevalence that has a disabling course for the patient. Episodes of heterotopic ossification may be provoked or may appear without any precipitating factor.

2. Currently available treatment is mainly symptomatic. More specific treatments are in research phases.

3. Regarding oral health, patients with FOP have the same prevalence of oral pathologies as the general population. The most prevalent complication is ankylosis of the TMJ with mouth opening limitation. This causes nutritional problems due to inability to eat and also limitation of access to the oral cavity for self-oral hygiene.

4. Dental treatment on these patients requires, in many occasions, a multidisciplinary and trained team. Control of pain by local anesthesia may not always be possible, truncal anesthesia is a technique that is prohibited due to the risk of ossification after muscle puncture. In these cases, general anesthesia is the best option.

5. It is important to avoid excessive stretching of the TMJ, which is why it is necessary to make changes to the access manoeuvres for both caries and extractions or any type of treatment, where in many cases the only access is the buccal surface.

6. There is a significant lack of scientific studies about oral management of patients with FOP, and very few cases described in literature. More research work should be done to establish a clinical protocol of action for dentists on these patients.

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