orphanaesthesia

Anaesthesia recommendations for

Fibrodysplasia ossificans progressiva

Disease name: Fibrodysplasia ossificans progressiva

ICD 10: M61.1

Synonyms: FOP, Münchmeyer's disease, Stone Age Man Disease

Disease summary: Fibrodysplasia ossificans progressiva (FOP) is a rare, progressive, and disabling autosomal dominant disorder of extraskeletal endochondral ossification, with complete penetrance but variable expression. FOP occurs with a prevalence of 0.36 to 0.61 per million. There are no predisposing ethnic or geographic factors. The current estimated number of patients is 2500, of whom 600 are known.

All muscles can be affected, except for the diaphragm, tongue, extraocular, and laryngeal muscles which are spared from heterotopic ossification; cardiac and smooth muscles are also not affected. Individuals with FOP appear normal at birth except for malformations of the great toes (Hallux valgus, shortening of the first ray, monophalangism). During the first decade of life, inflammatory soft tissue swellings, also known as flare-ups, transform skeletal muscles and connective tissues into a second skeleton of heterotopic bone that progressively immobilizes all of the joints of the axial and appendicular skeleton. Flare-ups may occur spontaneously but can be precipitated by misplaced venipuncture, soft tissue injury, muscle fatigue, intramuscular injection, biopsy or excision of heterotopic bone, viral illnesses, routine dental therapy, and injection of local anaesthetics during dental procedures.

Pathophysiologically, FOP is associated with alterations in the ACVR1 gene (activin type 1 receptor, also called ALK2), which encodes the receptor for the bone morphogenetic protein (BMP). A predominant mutation c.617G > A (p.Arg206His), found in about 90% of patients, is associated with the "classic" forms: abnormal first toe, first muscle ossification before age 10, and minor extramuscular or extraosseous signs. In 2009, atypical forms were described, referred to as FOP "variant" and FOP "plus." "Variant" FOP is characterized by normality of the great toes or, in contrast, severe impairment of the fingers. The "plus" forms are defined by the combination of a classic FOP with other signs (marfanoid appearance, central nervous system malformations, craniopharyngeomas and brainstem gliomas, endocrine disorders, ophthalmologic, dental and urogenital anomalies, aregenerative anemia).

All sporadic and familial cases of FOP have heterozygous activating mutations in activin receptor IA/activin-like kinase-2 (ACVR1/ALK2), a receptor for type I bone morphogenetic protein (BMP).

Disease flare-ups are episodic; immobility is cumulative and irreversible. Heterotopic ossification usually begins by ten years of age with neck and shoulder involvement. The temporomandibular joints may be involved early and are vulnerable to trauma at any age. The median lifespan is 40 years; death results most commonly from complications of thoracic insufficiency syndrome or pneumonia. A few deaths have been attributed to complications of

general anaesthesia. At the present time, no medical or surgical intervention can alter the natural course of FOP. Anaesthetic management for patients with FOP is challenging. Cervical spine fusion, ankylosis of the temporomandibular joints, thoracic insufficiency syndrome, restrictive chest wall disease, and sensitivity to oral trauma complicate airway management and anaesthesia.

Possible future treatment of FOP will likely rely on interventions that modulate the overactive ACVR1/ALK2 pathway or specifically block postnatal heterotrophic enchondral ossification. Current treatment focuses on early diagnosis, careful avoidance of injury or iatrogenic damage, symptomatic relief of painful episodes, and optimization of residual function.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Emergency information

A	**AIRWAY / ANAESTHETIC TECHNIQUE**	Difficult mask ventilation, limited mouth opening, oropharyngeal fusion, restrictive lung disease, awake nasal fibre-optic intubation is advised, regional anaesthesia is contraindicated HANDLE WITH CARE
B	**BLOOD PRODUCTS (COAGULATION)**	increased risk of thrombo-embolic complications
C	**CIRCULATION**	Clustered incidence of restrictive lung disease, pneumonia, thoracic insufficiency syndrome, and right-ventricular heart failure
D	**DRUGS**	Premedication should be avoided, promethazine or clonidine may represent alternative preparations succinylcholine should be avoided (risk of hyperkalaemia) cortisone supplementation
E	**EQUIPMENT**	variety of support materials, intensive care monitoring post-operative

Typical surgery

Numerous anaesthetics for dental rehabilitation, teeth extractions, and oral abscess drainages have been reported. Less common surgeries that have been reported include dilation and curettage, eye evisceration repair, femur and spine fracture correction, hysterectomy, pelvic mass excision, craniotomy for brainstem lesion, and osteomyelitis debridement.

Surgeries undertaken to correct complications caused by heterotopic bone formation are not advised unless the deformity is extraordinarily life or limb threatening. Interventions to correct bony formations and joint deformations often result in worsening of the disease due to reactive heterotopic bone formation at the surgical sites. FOP patients have, however, undergone successful corrective surgeries for chin-on-chest deformity, thoracic spinal canal stenosis, ulna-carpal bar, and hip ankylosis. These surgeries can be technically challenging and have been known to result in large amounts of blood loss. Furthermore, any surgery where connective tissue is manipulated may result in postoperative heterotopic ossification. Risks and benefits must be carefully weighed before proceeding with surgeries.

Type of anaesthesia

FOP patients often have temporomandibular joint ankylosis and cervical spine fusion; their airways can be difficult to manage. Three cases of perioperative “cannot ventilate, cannot

intubate" situations have been reported. Sedation should be performed with extreme caution, and general anaesthesia with an endotracheal tube is recommended. Traditional airway manoeuvres (i.e. jaw thrust) to alleviate obstruction or mask ventilation may not be successful. Laryngeal mask airway placement may be impossible in cases of limited mouth opening. Patients with restrictive lung disease may have limited physiological reserve. Additionally, direct laryngoscopy with a blade may traumatize temporomandibular joints and cause a flare-up, which may permanently decrease mouth opening. For the above reasons, an awake nasal fiberoptic intubation before induction of general anesthesia is advised.

Neuraxial anaesthesia is contraindicated in FOP patients due to the risk of heterotopic ossification in the spinal cord area triggered by trauma from spinal or epidural needle insertion. Regional anesthesia is relatively contraindicated; heterotopic ossification surrounding the area of needle placement is a concern. A successful and uncomplicated ultrasound-guided ankle block has been performed in an FOP patient. The anaesthesiologist limited local anesthetic injection to the epifascial tissue layer. Regional anesthesia may be a reasonable choice if the technique does not disrupt skeletal muscles or connective tissues, which are susceptible to pathologic ossification.

Routine injections of local anesthetic for dental procedures, especially mandibular blocks, should not be used because they have been shown to precipitate flare-ups and cause fusion of the temporomandibular joints.

Necessary additional pre-operative testing (beside standard care)

FOP patients are susceptible to restrictive lung disease, pneumonia, thoracic insufficiency syndrome, and right-ventricular heart failure. Depending on the functional status of the patient and the risk level of the surgery, pulmonary and cardiac evaluations may be necessary to guide management decisions.

Chest radiographs can provide evidence of atlantooccipital instability or deformity. In addition, pulmonary infections can be detected.

There is an indication for quantification of lung function and gas exchange (spirometry, blood gas analysis, CO diffusion capacity).

Routine biochemical tests are usually normal, although serum alkaline phosphatase activity and erythrocyte sedimentation rate (ESR) may be elevated, especially during a flare-up of disease. Elevation of C-reactive protein is a specific test for monitoring the acute inflammatory phase of heterotopic ossification or other occult infections.

Preoperative anamnestic assessment of exercise capacity (metabolic equivalent) is often not possible in immobilized patients.

Particular preparation for airway management

There have been three reported cases of anaesthesia providers not being able to ventilate or intubate an FOP patient. The recommendation is that an awake, nasal fibre-optic intubation before induction of general anaesthesia be considered the preferred, primary approach. This recommendation is based on: 1) frequently challenging airway anatomy and 2) the potential risk of trauma and heterotopic ossification of the temporomandibular joints from overstretching of the jaw with direct laryngoscopy.

Successful tracheal intubations after induction of general anaesthesia and using a video-laryngoscope have been reported. These patients had normal mouth opening and care was taken not to overstretch their jaws. Patients must be carefully selected for this technique. The extent of jaw movement should be measured preoperatively and should not be exceeded during airway instrumentation.

Preoperative bronchoscopic assessment of the supraglottic and infraglottic airway may be helpful in planning intraoperative airway instrumentation. Especially in the case of airway stenosis, various tube sizes must be kept on hand, since intubation is often only possible with small-lumen endotracheal tubes.

Emergency airway equipment should be available at the start of every anaesthetic. An otolaryngologist should be immediately available to assist with airway management during the procedure and to perform an emergency tracheostomy if needed.

Patients with FOP who are in chronic carbon dioxide retention and use unmonitored oxygen are at risk of suppression of respiratory drive due to sudden over-correction of oxygen tension. They should not use supplemental oxygen in an unmonitored environment.

Because of the increased risk of respiratory insufficiency, premedication should be avoided. If necessary, promethazine or clonidine may represent alternative preparations.

Particular preparation for transfusion or administration of blood products

Corrective orthopaedic surgeries may result in increased blood loss.

Particular preparation for anticoagulation

Immobilised patients may be at increased risk of thrombo-embolic complications.

Particular precautions for positioning, transportation and mobilisation

Positioning consideration is essential; patients' bodies are often fused in a rigid position. All pressure points must be padded and the neck supported. For this purpose, a wide variety of support materials (e.g. absorbent cotton, various sizes of support pillows) should be kept on hand. If a patient's cervical spine is fused in flexion, steep Trendelenburg positioning is often needed for adequate exposure for a dental procedure (the most common of surgeries). Positioning specifics for Trendelenburg include padding the patients' shoulders and securing the patients to the bed to ensure that their bodies do not shift on the table.

Interactions of chronic disease and anaesthesia medications

FOP patients often receive therapy with immunosuppressives, disease modifying antirheumatic drugs, NSAIDs or anti-infectives. In addition to increased susceptibility to infectious disease, typical drug side effects may have relevance to anesthesiologic management. NSAIDs in combination with additional anticoagulant therapy may increase the risk of bleeding. Appropriate pause intervals must be observed.

Anaesthetic procedure

Succinylcholine should be avoided because of risk of hyperkalaemia due to patient immobilisation.

A perioperative course of high dose corticosteroids (prednisolone and dexamethasone are used most commonly) can be considered and if indicated, should begin prior to the start of surgery to possibly mitigate heterotopic ossification stimuli.

In cases of long-term therapy with corticosteroids, peri-operative administration of additional hydrocortisone should be considered to avoid an Addison crisis.

FOP patients may have increased sensitivity to hypnotics, analgesics (especially opioids), and muscle relaxants. Since the duration of action of various substance groups may be prolonged, short-acting preparations may be advantageous (e.g., propofol, remimazolam, remifentanil). Suxamethonium should be avoided in immobilized patients.

Neuromuscular monitoring for intraoperative control of the degree of relaxation and to exclude relaxant overload during extubation is mandatory. In high-risk patients, the use of rocuronium is recommended because of the targeted reversibility by sugammadex.

Particular or additional monitoring

Neuromuscular relaxometry should be used in addition to standard monitoring.

Possible complications

Possible complications include: 1) difficult airway management, 2) exacerbation of thoracic insufficiency syndrome, restrictive lung disease, or right-sided heart failure, 3) heterotopic ossification due to misplaced intravenous catheter, needle trauma, or tracheal intubation, 4) heterotopic ossification or neuropathy due to positioning pressure, 5) hyperkalemia from succinylcholine administration.

Post-operative care

Patients with severe cardiac or pulmonary disease are at high peri-operative risk and may require intensive care capacity postoperatively.

There is an increased risk of postoperative respiratory complications, especially after intraoperative administration of respiratory depressants or muscle relaxants. Close monitoring (vital signs, blood gas analysis), early mobilisation and the use of noninvasive ventilation can help to avoid severe gas exchange disorders.

Disease-related acute problems and effect on anaesthesia and recovery

None known or reported.

Ambulatory anaesthesia

Ambulatory anaesthesia is an option if surgery is minor and the patient is relatively healthy. However, ambulatory surgery should take place at a tertiary care institution with adequate resources to handle possible procedural complications.

Obstetrical anaesthesia

Neuraxial anaesthesia is contraindicated, as previously described in these recommendations.

References

1. Cohen RB, Hahn GV, Tabas JA, Peeper J, Levitz CL, Sando A, Sando N, Zasloff M, Kaplan FS. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. A study of forty-four patients. J Bone Joint Surg Am. 1993;75(2):215-9
2. Connor JM, Evans DA. Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients. J Bone Jt Surg 1982;64(1):76-83
3. Luchetti W, Cohen RB, Hahn GV, Rocke DM, Helpin M, Zasloff M, Kaplan FS. Severe restriction in jaw movement after routine injection of local anesthetic in patients who have fibrodysplasia ossificans progressiva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(1):21-5
4. Scarlett RF, Rocke DM, Kantanie S, Patel JB, Shore EM, Kaplan FS. Influenza-like viral illnesses and flare-ups of fibrodysplasia ossificans progressiva. Clin Orthop Relat Res. 2004;(423):275-9
5. Rogers JG, Geho WB. Fibrodysplasia ossificans progressiva. A survey of forty-two cases. J Bone Joint Surg Am. 1979;61(6A):909-14
6. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91
7. Kaplan FS, Glaser DL. Thoracic insufficiency syndrome in patients with fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab 2005;3(3-4):213-16
8. Kaplan FS, LeMerrer M, Glaser DL, Pignolo RJ, Goldsby RE, Kitterman JA, Groppe J, Shore EM. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol 2008;22(1):191-205
9. Neuromuscular blockade leads to difficult intubation for pediatric dental patient. Anesth Malprac Prev 2003;8(1):1-8
10. Wadenya R, Fulcher M, Grunwald T, Nussbaum B, Grunwald Z. A description of two surgical and anesthetic management techniques used for a patient with fibrodysplasia ossificans progressiva. Spec Care Dentist 2010;30(3):106-9
11. Santoro AS, Cooper MG, Cheng A. Failed intubation and failed oxygenation in a child. Anaesth Intensive Care 2012;40(6):1056-1058.
12. Vashisht R, Prosser D. Anesthesia in a child with fibrodysplasia ossificans progressiva. Paediatr Anaesth 2006;16(6):684-8
13. Singh A, Ayyalapu A, Keochekian A. Anesthetic management in fibrodysplasia ossificans progressiva (FOP): a case report. J Clin Anesth 2003;15(3):211-3
14. Shipton EA, Retief LW, Theron HD, de Bruin FA. Anaesthesia in myositis ossificans progressiva. A case report and clinical review. S Afr Med J 1985;67(1):26-8
15. Gorji R, Li F, Nastasi R, Stuart S. Fibrodysplasia ossificans progressiva: anesthetic management in complex orthopedic spine procedures. J Clin Anesth 2011;23(7):558-61
16. Newton MC, Allen PW, Ryan DC. Fibrodysplasia ossificans progressiva. Br J Anaesth 1990;64(2):246-50
17. Stark WH, Krechel SW, Eggers GW Jr. Anesthesia in 'stone man': myositis ossificans progressiva. J Clin Anesth 1990;2(5):332-5
18. Lininger TE, Brown EM, Brown M. General anesthesia and fibrodysplasia ossificans progressiva. Anesth Analg 1989;68(2):175-6
19. Tumolo M, Moscatelli A, Silvestri G. Anaesthetic management of a child with fibrodysplasia ossificans progressiva. Br J Anaesth 2006;97(5):701-3
20. Schober P, Krage R, Thöne D, Loer SA, Schwarte LA. Ultrasound-guided ankle block in stone man disease, fibrodysplasia ossificans progressiva. Anesth Analg 2009;109(3):988-90

21. Mori Y, Susami T, Haga N, Tamura K, Kanno Y, Saijo H, Takato T. Extraction of 6 molars under general anesthesia in patient with fibrodysplasia ossificans progressiva. J Oral Maxillofac Surg. 2011;69(7):1905-10

22. Grobelny BT, Rubin D, Fleischut P, Rubens E, Mack PF, Fink M, Placantonakis DG, Elowitz EH. Neurosurgical management of symptomatic thoracic spinal ossification in a patient with fibrodysplasia ossificans progressiva. J Neurosurg Spine 2012 Mar;16(3):285-8

23. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. Available at: https://www.ifopa.org/living-with-fop-menu/treatment-guidelines.html. Accessed May 30, 2014

24. Kilmartin E, Grunwald Z, Kaplan FS, Nussbaum BL. General anesthesia for dental procedures in patients with fibrodysplasia ossificans progressiva: a review of 42 cases in 30 patients. Anesth Analg 2014 Feb;118(2):298-301

25. Thornton YS, Birnbaum SJ, Lebowitz N. A viable pregnancy in a patient with myositis ossificans progressiva. Am J Obstet Gynecol 1987 Mar;156(3):577-8

26. Corfield L, Hampton R, McCullough CJ. Wrist arthrodesis following ulnar bar excision in fibrodysplasia ossificans progressiva. J Hand Surg Br 2000 Apr;25(2):223-4

27. Benetos IS, Mavrogenis AF, Themistocleous GS, Kanellopoulos AD, Papagelopoulos PJ, Soucacos PN. Optimal treatment of fibrodysplasia ossificans progressiva with surgical excision of heterotopic bone, indomethacin, and irradiation. J Surg Orthop Adv 2006 Summer;15(2):99-104.

28. J. Paysala C, Sarretb E, Merlina R, Ravazzoloc R, Bocciardic J, M. Garcierd S, Monnote F, Laffarguef G, Baujate S, Echaubarda; 14 April 2017

29. R.RachkidiI.GhanemF.DagherK.Kharrat, Received 31 March 2007, Accepted 6 January 2008, Available online 5 March 2008.

30. Pediatr Endocrinol Rev. Author manuscript; available in PMC 2014 Jun 1.

31. Published in final edited form as: Pediatr Endocrinol Rev. 2013 Jun; 10(0 2): 437–448.

32. Schieren M, Wappler F, Anästhesie bei Haut-, Bindegewebs- und muskuloskeletalen Erkrankungen. In: Zacharowski K, Marx G, Hrsg. Checkliste Anästhesie. 1. Auflage. Stuttgart: Thieme; 2021.

Date last modified: **August 2022**

This recommendation was prepared by:

Zvi Grunwald, Anaesthesiologist, Thomas Jefferson University and Hospitals, Philadelphia, USA

Elaine Kilmartin, Anaesthesiologist, Thomas Jefferson University and Hospitals, Philadelphia, USA

Anna Rabinowitz, Anaesthesiologist, Jefferson Medical College, Philadelphia, USA

Frederick S. Kaplan, Departments of Orthopaedic Surgery and Medicine, Perelman School of Medicine, Philadelphia, USA

Saskia Lehmann, Anaesthesia Registrar, Erlangen University Hospital, Erlangen, Germany (Author update)
saskia.lehmann@uk-erlangen.de

Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

This recommendation was reviewed by:

Andrea Santoro, Paediatric Anaesthesist, The Children's Hospital at Westmead, Westmead, Australia
andrea.santoro@health.nsw.gov.au

Rolf Morhart, Paediatrician, Klinikum Garmisch-Partenkirchen GmbH, Germany
Rolf.Morhart@klinikum-gap.de

Johannes Prottengeier, Anaesthetist, Erlangen University Hospital, Erlangen, Germany
Johannes.prottengeier@uk-erlangen.de

Disclosure The reviewers have no financial or other competing interest to disclose.

Editorial review update 2022:

Johannes Prottengeier, Anaesthetist, Erlangen University Hospital, Erlangen, Germany
Johannes.prottengeier@uk-erlangen.de