

Anaesthesia recommendations for **Freeman-Burian syndrome**

Disease name: Freeman-Burian syndrome

ICD 10: Q87.0

Synonyms: Freeman-Sheldon syndrome, Whistling face syndrome, distal arthrogryposis type 2A, craniocarpotarsal dystrophy, craniocarpotarsal dysplasia, cranio-facio-corporal syndrome

Disease summary: Freeman-Burian syndrome (FBS) is a congenital myopathic craniofacial syndrome, with extra-craniofacial features in most cases. Genotype-correlated clinical diagnostic criteria for FBS include: microstomia, whistling face appearance (pursed lips), H or V-shaped chin defect, prominent nasolabial folds, and multiple contractures of the hands and feet. Limb malformations accepted in the diagnostic criteria for FBS include two or more of the following: talipes equinovarus, metatarsus varus, vertical talus, talipes equinovarus, calcaneovalgus, camptodactyly, ulnar deviation of wrists and fingers, overlapping fingers or toes, and hypoplastic or absent interphalangeal creases. Spinal deformities, metabolic and gastroenterological problems, other craniofacial malformations, and visual and auditory impairments are frequent findings in FBS. Some individuals present with minimal malformation; rarely patients have died during infancy as a result of severe respiratory complications. Autosomal dominant inheritance is established, but expression is often from new allelic variation. There is no apparent sex, ethnic, or geographical preference, and environmental and parental factors are not implicated in pathogenesis.

Medicine is in constant progress; new knowledge may not be in this recommendation.



Recommendations are not rules or laws; they only guide clinical decision-making.

Every patient is unique; individual circumstances must guide clinical care.

The diagnosis may be wrong; if questionable, the diagnosis should be confirmed.



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Disease background

Freeman-Burian syndrome (FBS; MIM 193700), formerly Freeman-Sheldon syndrome [1] and often referred to as distal arthrogryposis type 2A, craniocarpotarsal dysplasia or dystrophy, or whistling face syndrome, is a myopathic craniofacial syndrome [2]. FBS is originally described by Freeman and Sheldon (1938) [3] and independently confirmed as a new entity by Burian (1963) [4]. The genotype-correlated clinical diagnostic criteria [5-7], requires the following: microstomia, whistling-face appearance (pursed lips), H or V-shaped chin defect, prominent nasolabial folds, and major contractures of two or more body regions, typically in the hands and feet. Limb malformations accepted in the diagnostic criteria of FBS and the distal arthrogryposes include two or more of the following: talipes equinovarus, metatarsus varus, vertical talus, talipes equinovarus, calcaneovalgus, camptodactyly, ulnar deviation of wrists and fingers, overlapping fingers or toes, and hypoplastic or absent interphalangeal creases [5-6]. Spinal deformities, gastroenterologic problems, and other craniofacial problems are frequent findings [5, 8]. Some individuals present with minimal malformation [9]. Rarely patients die during infancy, as a result of severe respiratory complications [10-11]. FBS is often confused with phenotypically similar but genotypically and histologically unique conditions [1-2, 5]. Differential diagnoses include distal arthrogryposis types 1, 2B, 3, 7, and 8; arthrogryposis multiplex congenita; Schwartz-Jampel syndrome; and non-syndromic distal contractures. Intelligence is normal in FBS, but patients with cranial vault abnormalities, such as craniosynostosis, must be distinguished from patients with congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD; MIM 616266), a similar appearing but distinct condition from FBS. CLIFAHDD is caused by allelic variations in the sodium leak channel, non-selective (*NALCN*; MIM 611549) gene, located at 13q32.3-q33.1 [12]. FBS was distinguished from all other conditions by the presence of the pathognomonic craniofacial findings [1-2, 5-6], thus simplifying diagnosis. The presence of whistling face (pursed lips) alone or in combination with limb malformations was not diagnostic.

Inheritance of FBS is autosomal dominant, but expression is often sporadic [5]. Prevalence of FBS is unknown, mostly due to diagnostic uncertainty, 0.9 per million is often cited [13]. There appears to be neither sex nor ethnic preference. Environmental and parental factors are not implicated in pathogenesis. FBS can be caused by allelic variations in embryonic myosin heavy chain (*MYH3*; MIM 160720), all but two of which are predicted to impair adenosine triphosphate (ATP) binding to myosin [6]. Those thought to disrupt ATP binding are suggested to influence myophysiology during early development, attenuating muscle development and leaving residual defects of muscle contractures [6, 14]. In patients with FBS, white fibrous tissue within histologically normal muscle fibres and complete replacement of muscle by fibrous and adipose tissue is observed operatively [15]. In some areas, entire muscles are grossly and histologically normal [15]. The areas of fibrous tissue replacement behave like tendinous tissue, which is often released to reduce the contractures [1]. These operative findings correlate well with *in vitro* molecular myophysiology observations that show problems with the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power [16-18].

This recommendation, developed through literature review and clinical experience, aims to address the deficiency in available clinical guidance by providing essential outcomes-directed advice for evaluation and management of anaesthetic care for patients with FBS. The protocol for the systematic review and meta-analysis underpinning this recommendation development process is described elsewhere [19; PROSPERO: CRD42015024740]. Sponsored by the Freeman-Sheldon Research Group, Inc. and convened as the Guideline Development Task Force, guideline development and related activities were unfunded, and institutional review board oversight was provided by FSRG IRB #1. AGREE II and GRADE Guidelines [20, 21] were followed in the recommendation development process.

Typical surgeries

Patients with FBS frequently undergo numerous orthopaedic surgeries, because attempts at operative deformity correction have suboptimal results and require subsequent revision. Even craniofacial surgeries, which often have better outcomes, required revision, after eventual reformation of fibrous tissue contracting bands within normal muscle [1, 15]. Due to wide variability of FBS presentation and the paucity and poor quality of available literature, there are a great diversity of operative procedures to address the following conditions: ankle-foot complex contracture correction, spinal curvature correction (rod insertion and vertebral fusion), patellar instability correction, hand contracture correction, and craniofacial reconstruction, with oral commissuroplasties the most common surgery overall.

Type of anaesthesia

Although most case reports describe general anaesthesia, this is not meant to imply general anaesthesia is always needed in FBS. While the anaesthetic approach is ultimately dictated by patient safety, the patient's understanding and affect regarding surgery, and technical feasibility, it is possible and desirable to avoid pre-medication, sedation, and general anaesthesia for appropriately selected patients with FBS [15]. Though severe spinal deformities are common in FBS, this typically does not preclude epidural or spinal anaesthesia, which are still considered to have far fewer syndromic-associated challenges and complications and a more favourable safety profile over sedation and general anaesthesia. Whenever possible, consider and explore local, regional, spinal, and epidural anaesthesia with patients during the pre-anaesthetic consultation. Age is not necessarily a contraindication to any particular anaesthesia modality [15]. Many adults are poor candidates for local anaesthesia, and many children handle the experience very well [15]. Proper psychological preparation for patients undergoing surgery exclusively under local or regional anaesthesia does not differ substantively from any other pre-operative consent and preparation process [15].

Necessary additional pre-operative testing (beside standard care)

Anaesthetic care for patients with FBS presents a challenge and requires considerable pre-operative planning. Anaesthesiologists caring for the patient should always evaluate this patient well in advance of proposed procedures. A thorough and complete history should include questions about: current medications and allergies, reactive airways disease, gastro-oesophageal reflux disease (GERD), previous acute and chronic respiratory problems, prior anaesthesia and surgeries, seizures, and any symptoms of possible central nervous system dysfunction, especially increased intracranial pressure [22]. Examination includes: vital signs, mental status, airway, spinal, neurological, and cardiopulmonary assessments [22]. It is important to explain to the patient and family possible risks and ensure questions are answered and concerns fully addressed [15, 22]. Findings, concerns, and management plans must be discussed with the participating surgeons [22]. The preceding may seem obvious, but this is not the universal standard for assessment of potentially high-risk patients undergoing surgery. In some places where pre-operative evaluations are done in advance, a different anaesthesiologist conducts the evaluation than the one who cares for the patient on the day of surgery.

Some suggest that true malignant hyperthermia (MH) does not have an association with most myopathies in which anaesthetically-related hypermetabolic states resembling MH have been reported. Irrespective of the actual aetiology, an expanded metabolic panel and 12-lead

electrocardiogram are part of regular pre-operative screening for patients with FBS to prevent misinterpretation of a pre-existing status as being possibly related to MH changes. As arterial puncture for blood gases may be infeasible, point-of-care capillary blood testing can be helpful for baseline and subsequent assessment, when available. Though muscle biopsy for determination of MH susceptibility is a worthwhile assessment to make, it is not advised, due to the large muscle sample required for the *in vitro* caffeine-halothane contraction test. Genomic testing for the *RYR1* mutation is feasible, but the mutation is not associated with FBS. Case reports support a possible but low incidence of hyperthermia with triggering anaesthetics in patients with FBS, but there are also reports of patients who had no reaction when given volatile anaesthetic agents after previous non-triggering anaesthetic techniques. One case series reports 3 of 19 patients who developed MH with triggering volatile agents and another 2 who manifested only fever [5]. An MH-safe anaesthetic protocol (no volatile gasses or succinylcholine) of total intravenous anaesthesia with propofol and an opioid is easily accomplished and avoids any risk of anaesthetic-triggered rhabdomyolysis or MH. Notably, FBS is not associated with any cardiac muscle pathology.

Particular preparation for airway management

In patients with FBS, severe microstomia, micrognathia, immobile orofacial musculature, class II malocclusion, dental crowding, highly arched palate, and limited cervical spine flexibility may make endotracheal intubation and use of airway adjuncts difficult. The potential for thyroid and cricoid cartilage hypoplasia warrants a high level of concern for possibly securing emergency airway access via cricothyroidotomy, if that route of airway rescue is contemplated in the event of inability to secure the airway. Although there are reports of successful direct laryngoscopy, it is likely to be difficult, if not impossible. While some providers may elect to attempt use of a Laryngeal Mask Airway (LMA) to avoid a difficult intubation, the single case report in the literature lacks a sufficient description of the patient. LMA devices are not judged to be a reasonable airway management method in this challenging patient population, whose small oral aperture, decreased mouth opening, and oropharyngeal configuration may preclude the successful introduction and seating of an LMA. A smaller LMA device than typically used for the patient's age may be necessary. The possibility for GERD in this population may also modify intubation options[22], but appropriate fasting times and commonly prescribed GERD medical prophylaxis may reduce the risk.

Where available, a flexible fibre-optic bronchoscope guided technique is advised for non-emergent nasal or oral intubation. In institutions with limited facilities, blind nasal intubation may be attempted but risks airway trauma. These patients are most safely cared for in hospitals with the full range of airway equipment that may be needed. Patients can spontaneously ventilate with positive airway pressure support delivered through a soft nasopharyngeal airway in one nare, while fibre-optically guided intubation is performed through the other nare or mouth. If an LMA can be introduced, fibre-optic intubation can be performed through the LMA. Tracheotomy may be needed for emergent or unusually challenging intubations but may be technically challenging. Surgical back up should be arranged for the most difficult airways. When using a non-triggering MH anaesthetic protocol, airway management can be performed with intravenous infusion of either propofol or dexmedetomidine or both.

Particular preparation for transfusion or administration of blood products

No reports in the literature or known clinical experience indicate any unusual problems or needed precaution for patients with FBS needing transfusion or administration of any blood components. Distal extremity contractures and the consequent poor quality of veins may make establishing peripheral intravenous access challenging in many patients with FBS, and limited cervical mobility complicates neck vein access. Use of a small gauge catheter, 22 or less is generally required. Need for the use of a small gauge vascular catheter may impair transfusion, intravenous hydration, medication administration, and blood draw efforts. With increased use of ultrasound assisted peripheral vein cannulation, central line placement has a diminished role in providing vascular access for these patients but still may be necessary in a greater frequency than the general population.

Particular preparation for anticoagulation

While many patients have reduced pre-operative mobility and, therefore, are at a somewhat higher pre-operative thrombogenic risk, no reports in the literature or known clinical experience indicate any disorder of coagulation associated with FBS.

Particular precautions for positioning, transportation and mobilisation

Carefully evaluate patients pre-operatively to assess the extent of contractures. Any range of motion limitations found should be discussed with surgeons to plan the best positioning for the patient during surgery. Patients should always be placed in a position of respiratory comfort, with avoidance of unnatural mobilisation under anaesthesia, kept warm, and provided with generous padding to avoid pressure points. Use of padded dressings is recommended for areas at risk for pressure injury (sacrum if supine; breasts and iliac crests if prone). Thin patients and those with extended inpatient confinement are at higher risk for loss of skin integrity. Patients with skin complications should be seen by a plastic surgeon. Passive forced air heating systems should be used to maintain patient normothermia during anaesthesia and surgery, as many of these patients have reduced adipose tissue and are at increased risk of hypothermia.

Interactions of chronic disease and anaesthesia medications

There are no syndrome-specific chronic medications for patients with FBS, and there is no syndrome-specific treatment. Therapeutic interventions focus on improving functional outcomes. There is no cure, though FBS is believed to be non-progressive.

Anaesthetic procedure

Any non-MH triggering agents are safely used in patients with FBS, though some agents are used more extensively. Oral midazolam is routinely used for pre-medication, and intravenous midazolam is often used for mild procedural sedation. Induction of general anaesthesia is safely achieved with nitrous oxide, which is not a volatile MH-triggering gas. If maintenance of spontaneous respiration is essential, nitrous oxide is used in conjunction with ketamine to achieve and maintain surgical anaesthesia. If vascular access is established before

induction, propofol is frequently used for induction and maintenance of surgical anaesthesia. Intravenous infusion of either propofol or dexmedetomidine or both can be used to establish moderate sedation, with preservation of spontaneous ventilation for airway management and surgical anaesthesia. Spontaneous ventilation also can be maintained with nitrous oxide, ketamine, propofol, dexmedetomidine, or low-dose infusion of short-acting opioids, such as remifentanyl.

Lidocaine with or without epinephrine for local anaesthesia or bupivacaine (0.25 – 0.5%) for local anaesthesia, spinal, or epidural anaesthesia may be used. If performing spinal or epidural anaesthesia, a paediatric size needle and catheter is used, even for adults, as most patients with FBS are small. When using lidocaine or bupivacaine for local or regional anaesthesia with or without intravenous adjuvants, no special anaesthetic precautions are required. Peripheral nerve blocks, either single bolus injection or with catheter placement, may be used for extremity surgery and continued post-operatively for analgesia.

Particular or additional monitoring

While standard modern anaesthesia monitoring modalities are sufficient, vigilance is needed for monitoring in patients with FBS. Heart rate, respiratory rate and depth, and temperature are important warnings for an impending MH crisis. Hyperpyrexia without MH and rhabdomyolysis without hyperpyrexia may also present more frequently in this patient population. Muscle rigidity or relaxation is not a reliable indicator of anaesthesia depth, neuromuscular blockade effectiveness, or impending MH crisis, as syndromically affected muscles, especially those exhibiting overt contracture, are unaffected by anaesthesia and muscle relaxants. Oxygen saturation and end-tidal carbon dioxide are closely observed, as some patients have restrictive pulmonary disease or obstructive sleep apnoea. As clip sensors may not fit well, flexible adhesive oxygen saturation sensors are preferred and readily available in all institutions. They are applied circumferentially and fit any digit in the largest or smallest of patients. If a urinary catheter is used for monitoring, during a long surgery, or when epidural anaesthesia-analgesia is used, a paediatric size is chosen, even for adults, as most patients with FBS are small. The presence and character of dysphasia caused by orofacial anatomical abnormalities and muscle contractures should be documented before administration of any medication is noted to reduce potential mischaracterisation of dysphasia during pre-medication, sedation, or monitored anaesthesia when spoken patient responses are required.

Possible complications

Possible complications of general anaesthesia or sedation in patients with FBS include: pneumonia after general anaesthesia or deep sedation, hyperpyrexia without the malignant hyperthermia triad, malignant hyperthermia, rhabdomyolysis without hyperpyrexia, challenging peripheral vascular access, impaired operative access due to ineffectiveness of neuromuscular blockade or difficulty with positioning, and challenging oro-tracheal intubation due to anatomic abnormalities, including: severe microstomia, micrognathia, immobile orofacial musculature, class II malocclusion, dental crowding, highly arched palate, and limited cervical spine flexibility. Post-operative or post-sedation pneumonia may be caused by hypoventilation (atelectasis); meticulous anaesthetic care usually prevents aspiration. Severe spinal deformities may complicate epidural and spinal anaesthesia but rarely preclude it.

Post-operative care

Excessive analgesia with opioids and other potential respiratory depressants is an exceptional concern, as these agents potentiate the risk apnoea, over-sedation, and hypoventilation that may lead to post-operative respiratory distress. Non-steroidal anti-inflammatory medications and continuation of regional or epidural catheter techniques for post-operative analgesia provide the best pain control modalities for patients with FBS. Most patients are observed in the intensive or intermediate care unit for at least some time, especially after major surgery.

Disease-related acute problems and effect on anaesthesia and recovery

Acute consequences of potential decreased thoracic cage compliance from non-functioning intercostal muscles in patients with FBS are associated with predisposition to lower respiratory infections, with prolonged recovery. Aggressive antibiotic use and guaifenesin are warranted in the presence of positive physical examination findings of râles, rhonchi, wheezes, and pyrexia. Chest radiographs often are uninterpretable, with poor lung inflation due to decreased forced vital capacity and poor cough. In the advent of lower respiratory infection, sputum culture often is non-diagnostic, as many patients do not have adequate ability to cough. These patients require meticulous respiratory therapy in the post-operative period, which may include incentive spirometry, chest physiotherapy, with or without the use of a cough assist machine, and implementation of BiLevel Positive Airway Pressure, if airway obstruction or hypoventilation occur. If a culture is required, such as in empiric treatment failure, consider bronchoscopy to obtain a clean specimen. If general anaesthesia with intubation is necessary, the anaesthesiologist should use recruitment manoeuvres and endotracheal suctioning prior to extubation to maximise lung volume and reduce the risk of atelectasis. While not reported in humans and used uneventfully in FBS patients, a report suggests fluoroquinolones can trigger an MH crisis in susceptible individuals [23].

Special settings or types of anaesthesia

The general principles for the anaesthetic care of patients with FBS previously described apply with proper balancing of risks and benefits, to all types and settings of anaesthesia, including obstetric, ambulatory, or emergent.

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