Diagnosis, evaluation, and treatment in Freeman-Burian syndrome: clinical practice guideline for a rare and complex craniofacial syndrome

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- **Contributors**: More than a dozen physicians and surgeons from many specialties contributed to the discussion of the final recommendations. Families and patients also contributed their perspectives.
Learning Objectives

- **Identify** diagnostic and non-contributory findings of FBS.
- **Describe** how FBS affects global care considerations of the patient.
- **Discuss** potential medical, surgical, anesthetic, and psychosocial challenges patients with FBS may experience at various points.
- **Implement** new multidisciplinary clinical practice guidelines to improve care and clinical and functional outcomes for patients with FBS.
Background

- **Freeman-Burian syndrome (FBS):** Freeman-Sheldon syndrome, distal arthrogryposis type 2A, craniocarpotarsal dysplasia/dystrophy, whistling face syndrome
- **Described** by Freeman and Sheldon (1938) and independently confirmed as a new entity by Burian (1963)
- **Prevalence** is unknown (exceptionally rare).
- Congenital complex myopathic craniofacial syndrome
- **Diagnosis requires:** microstomia, whistling-face appearance (pursed lips), H or V-shaped chin defect, and prominent nasolabial folds.
Background: Clinical Findings

- **Other frequent deformities** include: additional craniofacial problems, limb malformations (camptodactyly, ulnar deviation, and talipes equinovarus), abnormal spinal curvatures, possibly chest wall deformities, and gastroenterologic problems.
- **Great clinical variability**: from very mild to quite severe
- **No data** on life-expectancy
- **Significant concerns regarding aspiration and pneumonia** for some patients (dysphagia, mouth breathing, poor tussive ability, functionally impaired intercostal muscles).
Background: Major Findings
Background: Differential Diagnosis

Patient with suspected Freeman-Burian syndrome (FBS)

Covered in present guideline

- Microstomia, prominent nasolabial folds, pursed lips (whistling face deformity), and H or V shaped chin dimple all present?
  - Yes: Probable FBS, refer to craniofacial team
  - No: Small mouth, prominent nasolabial folds, small but protuberant chin, and neck webbing all present?
    - No: Cleft palate, blepharoptosis, and scoliosis all present?
      - No: Major distal contractures in two or more areas and no craniofacial malformations present?
        - No: Refer to genetics for diagnosis
      - Yes: Probable DA3, refer to phsiatry, craniofacial team, and genetics
    - Yes: Probable SHS, refer to phsiatry and genetics

Not covered within scope of present guideline

- Probable DA1 or non-syndromic condition, refer to phsiatry and genetics
**Background: Etiology & Genetics**

- **Inheritance** is autosomal dominant; most cases are sporadic.
- No **biological gender or ethnic** preference is evident.
- No **environmental and parental factors** are implicated.
- **Allelic variations**: embryonic myosin heavy chain (MYH3)—may impair adenosine triphosphate binding to myosin.
- **If mental retardation, diagnosis is CLIFAHDD**, a distinct condition from FBS involving “congenital contractures of the limbs and face, hypotonia, and developmental delay” and caused by allelic variations in the sodium leak channel, non-selective.
Background: Pathology

- **White fibrous tissue that replaces normal muscle tissue** behaves like tendinous tissue, which is often operatively released to reduce the contractures.

- **Operative findings correlate well with in vitro findings** that show problems with the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power.

- **The most successful surgeries** are targeted releases of fibrotic replacement to achieve specified functional goals.

- **Surgeries are not focused on skeletal problems**; these fail.
Background: Craniofacial Skeleton
Methods & Materials

• Two systematic reviews (2015-2018):
  • Meta-analysis of individual patient data (FBS): 724 unique citations resulted in inclusion of 188 papers (304 patients); 101 papers (119 patients) reflected an FBS diagnosis.
  • Psychosocial concerns (FS and other non-intellectual impairing craniofacial malformation conditions): 1,462 unique citations resulted in 161 papers meeting the inclusion criteria.
• Expert consensus discussions panels (2006-2018) without formal deliberative process.
Guidelines: Craniofacial Surgeon

• New understanding of FBS has informed guidelines for an expanded role of the craniofacial surgeon, who now has primary responsibility for (1) evaluation and diagnosis, (2) counseling and education for families, (3) care and coordination, (4) longitudinal psychosocial support.

• **Families and patients** need to receive information directly from the craniofacial surgeon.

• Physiologically, **patients** need to receive most care from the craniofacial surgeon.
Guidelines: Early Life

• **Abortion is not recommended.** Mental retardation is not involved, and most individuals can do well with proper care.

• **Molecular testing of the patient is generally not recommended,** as there is no diagnostic or therapeutic benefit at this time.

• **Clinical genetics referral is generally not recommended,** as a meta-analysis indicates plastic surgeons have superior diagnostic accuracy for FBS over clinical geneticists.

• To address the **full range of rehabilitation concerns,** refer to physiatry rather than orthopedics.
Guidelines: Craniofacial Surgery

- Problems of **dysfunction of extraocular muscles** (blepharophimosis, blepharoptosis, and strabismus) must receive early operative intervention to preserve vision.
- Correction of **microstomia and improving nasal ventilation** should be considered.
- Craniofacial reconstruction should be considered to **improve speech and dysphagia**.
- Though oral hygiene and routine dental procedures are difficult in FBS, non-infected carious **permanent teeth should be restored to conserve bone mass**.
Guidelines: Acute Respiratory Problems

- Because of potential rapid-onset of complications, allergic rhinitis and all respiratory infections must be rapidly managed.
- For acute paranasal sinusitis, start patients on 3-4 day course of pseudoephedrine, guaifenesin, and an antihistimine.
- Afebrile patients with râles, rhonchi, or crackles in the lung field should be treated with moderate to high doses of guaifenesin for 3-5 days.
- Febrile patients with râles, rhonchi, or crackles in the lung field should be treated promptly with moderate to high doses of guaifenesin and appropriate antibiotic therapy.
Guidelines: Rehabilitation Care

• **Spirometry, sub- or maximal ventilation of oxygen, and resting metabolic rate testing** should be carried out to better understand respiratory efficiency and metabolic needs.

• Physiotherapy that takes into account the unique muscle problems in FBS should be undertaken to **prevent progression of abnormal spinal curvatures** that can lead to reduced intrathoracic and abdominal cavity volume.

• Patients must be encouraged and aided in living an active life.

• **Operative treatment of extremity deformities** is not recommended, as outcomes are typically very poor.
Guidelines: Rehabilitation Care

- **Early non-operative correction of hand deformities** should be the goal for optimal developmental, social, and physiological functioning, though potential remains for success with delayed therapy.

- Families and patients must receive a thorough explanation of **at-home hand exercises and brace use**, as suboptimal outcomes may result from poor compliance.

- For **feet resistant to non-operative treatment**, lower extremity prostheses without amputation should be offered.
Guidelines: Psychosocial Care

- Preschool and school-age patients should have objective intelligence and achievement testing before beginning school to improve access to appropriate academic services.
- In interpreting intelligence and achievement testing, sensory impairments must be considered, as these may artificially reduce some scores for patients.
Guidelines: Anesthesia Care

- **Avoidance of sedation and general anesthesia** should be considered to reduce complexity, unnecessary risk, and ensure a smoother post-operative course.
- **Flexible fibreoptic bronchoscope guided oral intubation** should be used.
- **Tracheotomy** may be needed for emergent or unusually challenging intubations but may be technically challenging.
Guidelines: Anesthesia Care

- Muscle rigidity must not be used as an indicator of anesthesia depth, effectiveness of neuromuscular blockade, or impending MH crisis, as the white fibrous tissue in muscles is unaffected by anesthesia and muscle relaxants.
- Use of opioids and other respiratory depressants must be limited, as these agents potentiate the risk of apnea, oversedation, and hypoventilation.
- Recruitment maneuvers and endotracheal suctioning must be used before exubation and meticulous respiratory therapy (e.g., incentive spirometry, chest physiotherapy, a cough assist machine, BiPAP) following extubation.
Thank you!

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  – https://www.researchgate.net/profile/Craig_Dufresne2
  – https://www.researchgate.net/profile/Mikaela_Poling
Diagnosis, Evaluation, and Treatment in Freeman-Burian Syndrome: Clinical Practice

Guideline for a Rare and Complex Craniofacial Syndrome

Joint Annual Meeting of the ACPA / ASCFS – Sunday, 2 May 2021

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Description

Freeman-Burian syndrome (FBS), formerly Freeman-Sheldon syndrome, is a well-known but exquisitely rare congenital craniofacial condition of myopathic origin. It frequently involves extremity contractures, abnormal spinal curvatures, and chest wall deformities. As treatment can be complex and patient outcomes remain suboptimal, we present an evidence- and experience-based clinical practice guideline whose goals are the (1) betterment of quality of life by mitigating deformities’ burden and (2) reduction of respiratory-related morbidity and mortality. Based on our decades of clinical experience with this unique and challenging condition, we feel much can be done to afford these patients a good and productive quality-of-life.

Keywords

Freeman-Sheldon syndrome; whistling face syndrome; arthrogryposis; myosin; congenital; guidelines; quality-of-life; craniofacial deformities; reconstructive surgical procedures; operative dentistry; anesthesia; corrective orthodontics; dysarthria; hearing loss; sinusitis; dysphagia; craniofacial surgeon; craniofacial team; craniofacial abnormalities; body physical appearance; interpersonal relations; self concept; social adjustment; social support
ABSTRACT

Background: Freeman-Burian syndrome (FBS), formerly Freeman-Sheldon syndrome, is a rare congenital complex myopathic craniofacial syndrome that frequently involves extremity joint deformities, abnormal spinal curvatures, and chest wall mechanical problems that, together with spinal deformities, impair pulmonary function. While potentially disabling, proper treatment can considerably improve patient outcomes, but clinical guidance does not exist, accurate up-to-date information limited, and clinical understanding of the syndrome at a professional and lay level is guided mostly by out-dated literature. The lack of available clinical guidance is known clinically to impair care and outcomes. To improve care and patient outcomes, we developed a clinical practice guideline.

Methods: From 2015-2018, we conducted two systematic reviews that included a meta-analysis of individual patient data. From 2006-2018, we also convened discussions to arrive at expert consensus among 10 experienced multidisciplinary participants, which included family and patient representatives. No formal deliberative procedure was used.

Results: Unsurprisingly, there was a great paucity of literature on FBS, and much of what was existent was of poor quality or not current. The resulting recommendations are heavily based on the clinical consensus of the participants, informed by appropriate literature. directed toward health status and quality of life improvement for affected individuals. Primary goals in evaluation and management of FBS must be the (1) betterment of quality of life by mitigating deformities’ burden and (2) reducing respiratory-related morbidity and mortality. Goals are best achieved with a combination of limited surgical procedures and an emphasis on therapeutic and maintenance physiotherapy, guided by a craniofacial team.

Conclusion: In FBS, craniofacial muscles may be preferentially impacted by fibrous tissue replacement. The lack of available objective data should not reduce clinical vigilance to the possibility that fibrous tissue replacement may influence almost any aspect of the patient’s presentation, thus necessitating non-standard treatment deviations. Based on our decades of
experience with this challenging patient population, we feel much can be done to afford FBS patients a good and productive quality of life through exquisite medical surveillance, rapid intervention in acute upper respiratory disturbances, conservative operative intervention, and longitudinal lifestyle structuring by the patients.
LEARNING OBJECTIVES

1. Identify diagnostic and non-contributory findings of FBS.
2. Describe how FBS affects global care considerations of the patient.
3. Discuss potential medical, surgical, anesthetic, and psychosocial challenges patients with FBS may experience at various points.
4. Implement new multidisciplinary clinical practice guidelines to improve care and clinical and functional outcomes for patients with FBS.
Associated Publications

Explanation & Elaboration


Systematic Review & Meta-Analysis


Systematic Review Protocols

- Poling MI, Dufresne CR. Epidemiology, prevention, diagnosis, treatment, and outcomes for psychosocial problems in patients and families affected by non-intellectually impairing...


Nomenclature & Classification


BIOSKETCH

Mikaela I Poling is an unpaid Research Assistant in plastic surgery. She has nearly two decades of experience in craniofacial clinical research, is an Associate Editor of the Journal of Pediatric Genetics and reviewer for a number of journals (including The Cleft Palate-Craniofacial Journal), has presented at several conferences, published over twenty papers, and led multidisciplinary research projects, including systematic reviews, a meta-analysis, and a clinical guideline task force. She has experience serving in various administrative, leadership, and community-engagement roles. In the early 2000s, she began mentored field research in limnology, geohydrology, and craniofacial surgery. She earned her undergraduate degree in history, with a specialization in modern Western military medicine and surgery. During college and while developing a long-range independent research plan with mentors in general surgery and plastic and craniofacial surgery, she completed several medical school clerkships. In particular, she gained supervised clinical experience caring for plastic surgery patients with full-thickness skin loss and multiple comorbidities. After completing undergraduate studies, she pursued advanced training in a clinical and applied physiology research fellowship. In this mentored setting, she continued her earlier work, obtaining a broad knowledgebase of human subjects research management and completing a graduate-level thesis, most of which has been published or is in review. Since 2016, she has been working with academic craniofacial surgeon, Craig R Dufresne, on projects of mutual interest. Together, they have presented and published work on Freeman-Burian syndrome, free dermal fat autografting for complex craniofacial wounds, and other topics.