

Freeman-Sheldon syndrome

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Creation Date: March 2005

Scientific Editor: Doctor Valérie Cormier-Daire

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Abstract

Freeman-Sheldon syndrome (FSS), also known as Whistling face syndrome, is a rare congenital disorder characterized by dysmorphic status combining bone anomalies and joint contractures with typical facies features. FSS is part of the nosologic group of the distal arthrogyposis. The three basic abnormalities are microstomia with pouting lips, camptodactyly with ulnar deviation of the hand and talipes equinovarus. The phenotype of FSS includes also scoliosis, H-shaped dimpling of the chin, deep nasolabial folds, and blepharophimosis. Dysphagia, failure to thrive, growth deficit, and life-threatening respiratory complications due to structural anomalies of the oropharynx and upper airways are frequent. Until 1990, 65 cases were reported in the literature. Both sexes are affected equally. Most reported cases of FSS occur sporadically with no family history of the disease, though there are reports of a specific pattern of either autosomal dominant or autosomal recessive inheritance. The etiology still remains unknown. Genetic counseling of affected individuals is imperative. Ultrasonographic evaluation (revealing abnormalities of the extremities and mouth) can help the prenatal diagnosis. Because of the clinical variability and rarity of FSS, there is no standard management protocol. Surgical correction of microstomia is important from aesthetic and functional points of view. Multiple, extensive orthopedic and plastic reconstructive surgery is often required.

Keywords

facial and skeletal abnormalities, microstomia, distal arthrogyposis, *TPM2*, *TNNI2*

Disease name/synonyms

Freeman-Sheldon syndrome
Whistling face-Windmill Vane Hand Syndrome
Craniocarpotarsal dystrophy
Craniocarpotarsal dysplasia
Arthrogyposis, distal, type2A (DA2A)

Definition

Freeman-Sheldon syndrome (FSS) is a rare congenital disorder defined by facial and skeletal abnormalities. It was firstly described by

Freeman and Sheldon in 1938 (1). FSS is part of the nosologic group of pathologies currently known as distal arthrogyposis (DA) (2), most closely related to distal arthrogyposis type 1 (DA1) (3).

Clinical description

FSS phenotype is similar to that of DA1. It is characterized by three basic abnormalities: microstomia with pouting lips, camptodactyly

with ulnar deviation of the hand and talipes equinovarus.

The characteristic facies typically include prominent supraorbital ridge, sunken eyes, telcanthus, short nose and colobomata of the nostrils, long philtrum, high narrow palate, and marked microstomia and microglossia. The facies are usually flattened with poor physiognomical expression. Fibrotic contractures of the facial muscles result in the characteristic "whistling face". In general, there is an "H"-shaped cutaneous dimpling on the chin.

Dysphagia, failure to thrive, growth deficit, and life-threatening respiratory complications due to structural anomalies of the oropharynx and upper airways are relatively frequent.

The hand deformities include ulnar deviation of the fingers, camptodactyly, first web space contracture, and hypoplasia of the thumb.

FSS was occasionally reported associated with mental retardation, especially in cases with combined important structural anomalies of the central nervous system. Children with FSS usually present speech impediments, often associated with hypoacusis.

Diagnostic methods

Since FSS is a morphologically well-defined syndrome, the diagnosis is based on the medical history and physical examination that reveal characteristic dysmorphic status combining bone anomalies and joint contractures with typical facies features.

Differential diagnosis

The differential diagnosis should exclude [arthrogryposis multiplex congenita](#) and particularly congenital windmill deformity of the fingers, which can also be accompanied by foot deformities.

Etiology

Most reported cases of FSS occur sporadically with no family history of the disease, though there are reports of a specific pattern of either autosomal dominant or autosomal recessive inheritance. A variant of FSS, DA2B (MIM 601680), is caused by mutations in *TNNI2*, encoding an isoform of troponin I (4). The prototypic DA, DA1 (MIM 108120), is caused by mutations *TPM2* (5,6). The mechanism(s) by which mutations in *TPM2* and *TNNI2* cause multiple congenital contractures is unclear. Recent study suggested that the etiology of congenital contractures in patients with sporadic disease may be different from that in patients with familial disease (4). The authors did not find mutations in *TNNI2* in any of the probands with

classical FSS; thus, they concluded that the etiology of FSS remains unknown (4).

Epidemiology

Until 1990 there were up to 65 cases reported in the literature (7). Both sexes are affected equally.

Genetic counseling

Genetic counseling of affected individuals is imperative. Recurrence risk of 25% should be considered for autosomal recessive inheritance.

Prenatal diagnosis

Until the gene for FSS is mapped, it is impossible to carry out prenatal diagnosis through direct DNA analysis. Ultrasonographic evaluation can help the prenatal diagnosis of FSS, as it was reported for 20-week fetus with a positive family history (8). It revealed abnormalities of the extremities and mouth.

Management including treatment

Because of the clinical variability and rarity of FSS, there is no standard management protocol. The foot and hand deformities are resistant to treatment and require consistent conservative and operative measures. Multiple, extensive orthopedic and plastic reconstructive surgery is often required. Surgical correction of microstomia is important from both aesthetic and functional points of view (food intake especially). Structural anomalies of the oropharynx and upper airways are a constant concern for general anesthesia. Tracheal intubation via direct laryngoscopy often cannot be carried out. The spine should be evaluated preoperatively to perform epidural/spinal anesthesia. Intravenous access may be difficult because of limb deformities and thickened subcutaneous tissues. Patients with FSS may be at increased risk for malignant hyperthermia and postoperative pulmonary complications. The follow-up of FSS pediatric patients requires support and special care including prolonged orthodontic and orthopedic treatment. Speech and hearing follow-up is also beneficial.

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