CASE REPORT

Freeman-Sheldon syndrome in a 29-year-old woman presenting with rare and previously undescribed features

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SUMMARY

Described are previously unreported features presenting in a case of Freeman-Sheldon syndrome (FSS); these apparently unreported features may substantively inform current therapy and further research. While considered to be primarily a craniofacial syndrome, FSS is officially described as a myopathic distal arthrogryposis. Clinical diagnosis requires microstomia, whistling-face appearance (pursed lips), H-shaped chin dimpling, nasolabial folds, and two or more contractures of hands and feet. Spinal deformities, metabolic and gastroenterological problems, other dysmorphic craniofacial characteristics, and visual and auditory impairments are frequent findings. Differential diagnoses include: distal arthrogryposis type 1, 2B (Sheldon-Hall syndrome) and 3; arthrogryposis multiplex congenita and isolated non-syndromic deformities. Expression is frequently from new allelic variation. Important implications exist for geneticists, neonatologists, paediatricians, plastic surgeons and others to facilitate patients' legitimate opportunity to meaningfully overcome functional limitations and become well. Despite complexities and complications, early craniofacial surgery and aggressive physiotherapy for limb contractures can achieve excellent outcomes for patients.

BACKGROUND

Freeman-Sheldon syndrome (FSS; MIM #193700), often referred to as distal arthrogryposis type 2A, craniocarpotarsal dysplasia or dystrophy, or whistling face-windmill vane hand syndrome, was originally described by Freeman and Sheldon.¹ While FSS is considered by many to be primarily a craniofacial syndrome, it is officially described as a type of myopathic distal arthrogryposis; clinical diagnosis requires the following: microstomia, whistling-face appearance (pursed lips), H-shaped chin dimpling, nasolabial folds, and two or more contractures of hands and feet.²⁻³ Spinal deformities, metabolic and gastroenterological problems, other dysmorphic craniofacial characteristics, and visual and auditory impairments are frequent findings.²⁻³ Some individuals present with minimal malformation;⁴ rarely, patients die during infancy as a result of severe central nervous system involvement⁵ or respiratory complications.⁶

Most familial cases are by autosomal dominant inheritance, but expression is often from new allelic variation.⁷ Frequency of FSS is unknown, mostly due to diagnostic uncertainty. There appears to be

neither sex nor ethnic preference. Preconception testing of polar bodies and prenatal diagnosis can be achieved by targeted mutation testing of the myosin heavy chain 3 gene (*MYH3*; MIM #160720). Prenatal ultrasound can be useful, but a normal ultrasound should not be considered to rule out the condition entirely. Environmental and parental factors are not implicated in pathogenesis. Potential for malignant hyperthermia (MH) and difficult intubation and vascular access complicate surgical planning.

Described are features, as yet unreported, presenting in the most severe case of FSS, of which the authors are aware. These apparently unreported features, which were not found elsewhere in a recently completed systematic review and meta-analysis (Morales, *et al.* Unpublished. 2015), may substantively inform current therapy and further research. Having received institutional review board approval from FSRG IRB #1, signed informed consent for publication and of descriptions and photographs was obtained from proband and family. Despite complexities and complications, early craniofacial surgery and aggressive physiotherapy for limb contractures can achieve excellent outcomes for patients. Important implications exist for plastic surgeons, paediatricians, geneticists and others, to facilitate patients' legitimate opportunity to meaningfully overcome functional limitations and become well.

Allelic variation and abnormal muscle physiology

Toydemir *et al*⁸ presented allelic variations in *MYH3* causing classic FSS phenotype in their screening of 28 (21 sporadic and 7 familial) probands with FSS. In 20 patients (8 and 12 probands, respectively), missense allelic variations (R672C and R672H) caused substitution of arg672, an embryonic myosin residue retained postembryonically.⁸ Of the remaining six patients in whom they found allelic variations, three had missense private de novo (E498G and Y583S) or familial allelic variations (V825D); three other patients with sporadic expression had a de novo allelic variation (T178I), which is also found in Sheldon-Hall syndrome (SHS) and was thought to produce a severe phenotype;⁹ and two patients had no recognised allelic variations.⁸

Toydemir *et al*⁸ and Tajsharghi *et al*⁷ showed that the basic genetic defect indicated disrupted

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Figure 1 Photograph of the patient (front right) and her family (normal phenotypes).

Figure 2 Photograph before surgeries, at 2 years of age. The patient was told to smile and used her hands to push oral commissures upward, as hypoplastic facial musculature reduced ability to physiologically smile.

Figure 3 Comparison craniofacial (A and B) frontal and (D and E) lateral photographs (ages 2 and 20 years) and (C) frontal and (F) lateral CT images (22 years) showing Freeman-Sheldon syndrome associated physical features.

ATP binding to *MYH3*. It was unknown how this disrupted binding might have correlated to the phenotypes observed,⁸ but it was suggested to influence myophysiology during early development, producing joint contractures due to haploinsufficiency of *MYH3*'s product, and posteriorly to downregulation, a restitution of muscle development presents, leaving residual defects.^{7 10} Muscle cells and myofibrils of two patients with missense allelic variation R672C showed attenuated specific force, lengthened time to relaxation and higher baseline residual force.¹¹ This appeared to be due to a diminished number of myosin cross-bridges and attenuated detachment kinetics, and slow and incomplete deactivation of thin filaments during the latter part of contraction.¹¹

CASE PRESENTATION

The patient was a 29-year-old 46, XX female, first of three female siblings, born 2 weeks post-term via emergency caesarean

Table 1 The patient's Freeman-Sheldon syndrome features satisfying the Stevenson's diagnostic criteria

All required	Two or more required
Microstomia*	Ulnar deviation of the wrists and fingers
Pursed lips (whistling face)*	Camptodactyly
H-shaped chin dimpling	Hypoplastic or absent flexion creases
Prominent nasolabial folds	Overriding fingers at birth
	Talipes equinovarus†
	Vertical talus‡
	Metatarsus varus

*Oral commissurotomies, at ages 2 and 14 years, resulted in limited temporary improvement in oral opening, modification of lip appearance, and chronic, uncontrollable external flow of oral secretions and sensory deficits.
†There was significant surgical modification of feet, including bilateral talectomies, leaving the feet immobile, heavily scarred with sensory and motor neurological defects, and poorly perfused, as evidenced by essentially non-palpable popliteal and pedal pulses.
‡Bilateral talectomies were performed at 6 years of age, as part of unsuccessful equinovarus correction.

Figure 4 Palmar view of right (A) and radial view of left (B) hand showing characteristic arthrogryposis-type features, and frontal photograph and CT image of legs and feet showing considerable surgical modification (C, D). Notice symmetrical appearance of hands with classic arthrogryposis features. There is minimal active extension of all digits, but grip is fair. There is severe adduction and overlapping of digits one and two. In the ankle-foot complex, there is ankylosis of the talocrural joint (left 160°; right 100°) and metatarsals 2–4. Weight bearing is on the anterolateral foot (proximal interphalangeal joints). Notice bilateral patellar subluxation with extension and tibiofemoral joint flexion contracture. There is also an approximately 30° lateral deviation from the origin of the quadriceps to patellar tendon insertion on the tibial tuberosity.

Figure 5 Plain chest radiographs (A) anterior-posterior and (B) lateral showing new and previously associated Freeman-Sheldon syndrome physical features. For the anterior-posterior view, the patient was seated to eliminate bias from uneven lower extremity length. Cobb's angle for scoliosis, which showed a maximum curvature at 9th and 10th ribs; lordosis extending from T1 to sacrum; and length of hyperintense opacified vertical ridge following the right dorsal mid-clavicular line from the inferior scapular border to the inferior costal margin, are marked.

Table 2 The patient's common Freeman-Sheldon syndrome features (from 'DA2A Clinical Synopsis' in *Online Mendelian Inheritance in Man*)²

Failure to thrive (infancy)*
Postnatal growth deficiency
Full forehead
Mask-like facies
Long philtrum
Flat face
Deep set eyes
Strabismus†
Blepharophimosis
Ptosis (upper eyelid)‡
Broad nasal bridge
Small nose
Hypoplastic alae nasi
Short neck§
Scoliosis¶
Shoulder contractures
Knee contractures
Cortical thumbs
Contracted toes
Thickened skin over flexor surface of proximal phalanges
Mild muscle weakness
Skeletal muscle biopsy shows fibre size variability
Increased interstitial connective tissue
Nasal speech
Hyperpyrexia, usually associated with anaesthesia
Malignant hyperthermia

*Failure-to-thrive seemed to persist beyond infancy, as evidenced by the patient's malnourished appearing habitus despite adequate oral intake and use of supplemental nutritional drinks.

†The patient had a mild right internal strabismus.

‡Upper eyelid ptosis was improved by bilateral modified therapeutic blepharoplasty.

§Our patient exhibited a markedly short neck of 8 cm from T1 to occiput base.

¶There was rotational thoracic scoliosis (Cobb's angle 53°) and thoracolumbar lordosis (Cobb's angle 80°).

Table 3 The patient's less common and rare*Freeman-Sheldon syndrome (FSS) features

Extreme neck contracture manifested by left atrophy and right hypertrophy of the sternocleidomastoid muscle and platysma, pulling the mandible inferiorly ^{13 14}
Non-functional intercostal muscles, resulting in laboured resting ventilation dependent on diaphragmatic breathing, with activation of secondary accessory muscles ¹³
Right axis deviation sometimes with spiking T waves on 12-lead ECG, suggesting right heart strain from chronic restrictive pulmonary disease ¹⁵
Eleven ribs bilaterally ^{6 16}
Patellar subluxation ¹⁷
Chronic depression, secondary to chronic illness, per Diagnostic and Statistical Manual of Mental Disorders 5 criteria, secondary to medical trauma ¹⁸
Posteriorly broad ribs ^{13 19}
Craniosynostosis (mild scaphocephaly)
Malocclusion, severe class II
Micrognathia
Microglossia
Narrow palate
Postero-inferior pinnae deviation
Ocular hypertelorism
Nystagmus
Dental crowding
Symmetrical subcutaneous elevations of medial frontal areas
Prominent supraciliary ridge
Low hairlines, with horizontal area of skeletal elevation paralleling frontal contour hairline
Straight mandibular rami
Severe dysphagia that did not improve with age, requiring a thin, puréed diet
Recurrent frontal headaches ³
Discrepancy in lower extremity length

*Features were considered rare, if there were two or less previous reports of the features in patients appearing to fulfil Stevenson's 2006 diagnostic criteria,³ discovered in a recently completed systematic review and meta-analysis (Morales, et al. Unpublished. 2015).

Figure 6 12-Lead resting ECG at 29 years of age showing sinus tachycardia of 109 bpm, right axis deviation and somewhat spiking T waves, all suggestive of right heart strain. Recording was made after the patient had been resting in the supine position >15 min and had not been engaged in strenuous physical activity. There is some artefact due to poor electrodes. Notably, 12-lead ECG monitoring, at the time this recording was made, showed rapidly varying heart rate of 82–215 bpm.

section, due to failure to progress, to a 28-year-old mother (gravid 1, para 1) and a 31-year-old father of Western and Central European descent. The patient's two siblings (now 19 and 16 years old) and parents (now 56 and 59 years old) had no overlapping findings with the patient (figure 1). The patient's perinatal measurements were 3.5 kg (weight) and 53.3 cm (length); Apgar scores were 8 and 9, at 1 and 5 min, respectively. Geneticist-confirmed diagnosis and discharge were days 2 and 21, respectively.

History included: polyhydramnios, without other pregnancy complications; neonatal complications of perinatal meconium staining (with secondary respiratory infection) and difficulty clearing the airway; moderate developmental delay, secondary to physical handicaps; episodic apnoea without cyanosis (first year), accompanied by difficulty with oral secretions, which had to be aspirated via nasogastric tube; recurrent otitis media and numerous pressure equalisation tube insertions (early childhood); recurrent sinusitis, bronchitis and pneumonia; non-painful difficult defaecation without hard faecal matter; and hyperpyrexia syndrome seemingly triggered by surgery (without MH triggering agents) and other non-operative unusual stress. The hyperpyrexia syndrome experienced by our patient (1) presented with the MH triad, (2) was more frequent in infancy, and (3) resulted in extreme post-episodic skeletal muscle fatigue and weakness that could last days.

While some patients with FSS experience failure-to-thrive in infancy, our patient experienced poor appetite until around 18 years of age and, despite eating a high-caloric and high-protein diet, continued to experience difficulty in maintaining adequate weight. Casting of the feet and bracing of the hands in infancy was not followed by physiotherapy, and corrections were lost. Beginning at 2 years of age (figures 2 and 3A, D), the patient had over 20 surgeries on feet, knees and craniofacial structures, most unsuccessful, resulting in deteriorated clinical status. At 22 years of age, the patient experienced an idiopathic, sudden-onset unilateral low-frequency conductive hearing loss without additional features or association, which spontaneously resolved after approximately 3 months.¹²

INVESTIGATIONS

Examination revealed a short, thin female (1.45 m and 30.844 kg, body mass index 14.7 kg/m²) with whistling-face appearance and striking lack of facial musculature, resulting in about 80% reduction of plasticity; along with required features³ (table 1 and figures 2–4); most of the common features (table 2 and figures 2–5); some infrequently reported findings (table 3; figures 3, 4 and 6); and features previously unassociated with FSS diagnosis (table 4; figures 5 and 7).

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for suspected FSS includes: distal arthrogryposis type 1, 2B (SHS—formerly described as Freeman-Sheldon variant) and 3 (Gordon syndrome); and isolated non-syndromic deformities. While molecular diagnosis was not economically possible for our patient and her family, the patient presented with the classic pathognomonic features of FSS,³ including H-shaped chin dimpling, microstomia, whistling-face (pursed lips) appearance and prominent

Table 4 Previously undescribed features in patients with Freeman-Sheldon syndrome of potential clinical and research value

Thyroid and cricoid cartilage hypoplasia
Vertical ridge of ossified elevation following the right dorsal midclavicular line from the inferior scapular border to the inferior costal margin
Left atrophy and right hypertrophy of the latissimus longus and right atrophy and left hypertrophy of the latissimus dorsi muscles
Paroxysmal resting tachycardia of typically 110–130 bpm, with a range of 56–215 bpm, without evidence of pathology on 12-lead ECG, 36 h Holter monitor, or transthoracic echocardiography
Severe hyperhidrosis (axillary, popliteal, medial thighs, anterior and posterior trunk, plantar surfaces and palmar surfaces)
High intelligence (Wechsler Intelligence Scale score 168)
Post-traumatic stress disorder, per Diagnostic and Statistical Manual of Mental Disorders 5 criteria, Secondary to medical trauma
Undersized external auditory canals
Secondary limitation of extra ocular movement

Figure 7 Transverse CT demonstrating thyroid and cricoid hypoplasia.

nasolabial folds, excluding the possibility of another diagnosis. Moreover, the families of our patient's parents denied possible consanguinity prior to their marriage, making autosomal inheritance seemingly less likely.

OUTCOME AND FOLLOW-UP

At latest presentation, trial physiotherapy in the hands had shown improvement,²⁰ and while patellar subluxation remained problematic, bilateral patellar tendon-bearing Symes prostheses

Patient's perspective

Experiencing this syndrome isn't what is bad—experiencing poor care that makes my condition worse because no one understands this syndrome is what is bad, but honestly, I couldn't care less about Freeman-Sheldon syndrome. It doesn't define me and never has; it simply doesn't factor in. What I think about are the practical, logistical things that are an issue at this point, such as when I want to go out somewhere I think about who I am going to get to walk around with me in case my knees go out. I probably am most annoyed by the instability of my knees, which does not even allow me to safely walk around on my own property. I would really like to do simple chores, join my family in working on our farm, go out in the forest and harvest some wild game to eat, or just walk about to enjoy nature. But, I don't think of this in terms of the syndrome; I see it as a discreet, solvable problem for which the syndrome is only a backdrop that must be considered. Another point of frustration is my facial appearance. No matter who you are, what you believe, or what you say you believe, everyone—including me—judges people by their face first. Sometimes a facial appearance can be transcended, but it's still an extra step that impedes communication, and it's a factor that always remains no matter how well the parties know each other—and it gets old after a while. Even if my knees were good, the communication barrier caused by my appearance is so considerable that I would still require someone to tag along with me—just to vouch for me and answer questions! But the experience of the syndrome hasn't been all bad. Because my face is so distinctive, people seem to remember me more easily, and that's been very helpful. Also, since the syndrome is really rare, that's given me audiences with some outstanding people in academic medicine, which has also paid dividends.

enabled ambulation, despite non-functional biological feet.²¹ Future therapeutic attention will focus on surgical correction of bilateral patellar subluxation, dysphagia, and a better understanding and management of energy expenditure.

DISCUSSION

FSS is a highly variable spectrum of related pathological entities, supported by allelic variation and phenotype correlation,⁹ about which relatively little is known and on which guidance is absent. While we feel present nosological classifications of FSS fail to consider the multiple anatomical and physiological findings, the previously unreported and previously reported rare features exhibited by our patient (table 4), together with our other experience with the syndrome, may highlight potentially important new, unrecognised aspects of FSS that bear diagnostic and therapeutic attention and could diminish nosological ambiguity.

While molecular diagnosis was not economically feasible for our patient and her family, 7% of clinical FSS phenotypes are unaccounted for by currently documented allelic variations,⁸ and some *MYH3*-associated allelic variations do not always produce an FSS phenotype. Our patient exceeded requirements of the strict criteria² (table 1), which has high sensitivity and

specificity of clinical diagnosis correlation to molecular diagnosis⁸ and genotype.⁹

Our findings of concomitant post-traumatic stress disorder and chronic depression highlight the underlying iatrogenic potential of extensive therapeutic activities when children present with a congenital global musculoskeletal syndrome. In our patient, paroxysmal tachycardia without pathology may have been related to the impaired ventilation caused by non-functional intercostal muscles¹³ and narrowed airway, and, more speculatively, the tachycardia may also be indicative of physiological compensatory process to overcome the deficit of myosin head ATP binding sites, which may indirectly be supported by our patient's inability to gain weight despite a high-caloric and high-protein diet. Our patient later developed ECG evidence of right heart stress,¹⁵ which supports an impaired ventilation hypothesis. We are investigating resting energy consumption and energy requirements during activity in FSS with a case-control cohort study (NCT01306994). Irrespective of the pathogenesis, 12-lead ECG should be part of regular preoperative screening for all patients with FSS, to prevent misdiagnosis as MH-related tachycardia.

Presence of thyroid and cricoid cartilage hypoplasia in our patient warrants an important contraindication for emergency airway via cricothyroidotomy, and should be considered as a possibility in patients with FSS—a population notable for difficult endotracheal intubation—and sought in patients who may require a secure airway. In our patient, severe micrognathia, together with hypoplastic thyroid and cricoid cartilages, appeared to result from insufficient myological tension during development.

The vertical ridge of ossified elevation following the right dorsal midclavicular line from the inferior scapular border to the inferior costal margin may contribute to the understanding of chest pathology in our patient, as it obviously limited the right costal movement. Similar findings should be sought in other patients with FSS. Left atrophy and right hypertrophy of the latissimus longus and right atrophy and left hypertrophy of the latissimus dorsi muscles, respectively, may suggest pathogenesis of later progression of spinal deformities, but more investigation is needed. Although physiologically unlikely, this finding could be a consequence, not precipitant, of the scoliosis. The finding of highly localised variation in syndromic variation in muscles should prompt careful discriminatory analysis of each muscle in any region that may be the target of therapy and guide further research. We found an essentially unaffected vastus lateralis muscle.¹³ Pathogenic implications of severe, functionally limiting hyperhidrosis in our patient are not immediately clear and may be unrelated to FSS, though no family members experienced this symptom. Laboratory investigations yielded no helpful data, and hyperhidrosis showed no concomitant findings and was unassociated with ambient environmental conditions or the patient's mental state. Undersized external auditory canals and secondary limitation of extraocular movement both seem to relate to the myopathic basis of the syndrome and do not seem to have been previously reported.

In two intelligence and achievement test results, to which we had access to, our patient performed markedly better on verbal than reading portions; this is important to consider, as our patient was legally blind but not hearing impaired. Sensory impairments may have artificially reduced some scores for patients with FSS who were considered 'average' or 'borderline'. While certain patients with FSS with mental retardation, hypotonia and early death exhibit missense allelic variations in the sodium leak channel, non-selective (NALCN),²² our clinical

Learning points

- ▶ Early nutritional consultation and monitoring is requisite to ensuring adequate nutritional intake in light of dysphagia and failure-to-thrive, which can persist beyond infancy and childhood.
- ▶ Irrespective of occurrence of a malignant hyperthermia crisis, anaesthesia is always more challenging and requires considerable planning and care.
- ▶ Parental education and support is critical, as many children with Freeman-Sheldon syndrome (FSS) require high-intensity care and proactive monitoring of health and developmental progress.
- ▶ Early psychiatric consultation for the patient may help mitigate lasting psychiatric consequences of invasive early-life therapeutic activities and stigma of congenital malformations.
- ▶ As bronchitis and pneumonia are frequent complications of upper respiratory infection in FSS, patients with FSS should receive proactive pulmonary surveillance to prevent or limit occurrence of lower respiratory infections and long-term consequences of recurrence.

experience with many patients of different ages and socioeconomic backgrounds has shown that higher intelligence, relative to other family members, may represent a strong feature in a subset of patients with FSS without NALCN allelic variations or repeated hypoxia. Higher intelligence in this subset of patients with FSS may be the first association of higher intelligence with a pathological entity, and after many years of observation, we feel this possible association can no longer be ignored and warrants further inquiry. We are continuing to investigate intellectual function in patients with FSS in an international multicentre cohort study (NCT01307475), as well as examining other poorly understood findings displayed by our patient.

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Contributors All the authors have qualified for authorship under ICMJE guidelines, reviewed the final version of the manuscript, agree to be accountable for all aspects of the work, and have no conflicts of interest. RLC and MIP were the primary originators and were involved in collection, analysis and interpretation of clinical data. ALP and RRTR, who both died before the manuscript could be submitted, and RJM, also participated in writing the manuscript and in collection, analysis and

interpretation of clinical data. AM was involved in substantive text revisions to the manuscript and analysis and interpretation of clinical data.

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