CASE REPORT

Preliminary experience with delayed non-operative therapy of multiple hand and wrist contractures in a woman with Freeman-Sheldon syndrome, at ages 24 and 28 years

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SUMMARY

We describe two proof-of-concept trials of delayed non-operative therapy of multiple hand and wrist contractures in a woman with a severe expression of Freeman-Sheldon syndrome (FSS), at ages 24 and 28 years. Having presented as an infant to a university referral centre, passive correction was not accompanied by strengthening exercises, and correction was lost. FSS is described as a myopathic distal arthrogryposis; diagnosis requires the following: microstomia, whistling face appearance, H-shaped chin dimpling, nasolabial folds, and multiple hand and foot contractures. Spinal deformities, metabolic and gastroenterological problems, other craniofacial characteristics, and visual and auditory impairments, are frequent findings. To avoid possible FSS-associated complications of malignant hyperthermia and difficult intubation, and to reduce or eliminate need for surgery, we proceeded with passive manipulation without anaesthesia or sedation. We believe this is the first report of attempted non-operative correction of multiple hand and wrist contractures in an adult with FSS.

BACKGROUND

We describe two proof-of-concept trials of delayed non-operative therapy of multiple hand and wrist contractures in a woman with a severe expression of Freeman-Sheldon syndrome (FSS; MIM #193700), at ages 24 and 28 years. Having initially presented as an infant to a university referral centre, passive correction was not accompanied by strengthening exercises, and, essentially, all correction was lost. To avoid possible FSS-associated complications of malignant hyperthermia (MH) and difficult intubation, and to reduce or eliminate need for surgery, we proceeded with passive manipulation without anaesthesia or sedation. In the setting of poorly understood FSS-associated myopathology, avoidance of surgery in the extremities is advisable.

Often referred to as distal arthrogryposis type 2A, craniocarpotarsal dysplasia or dystrophy, or whistling face-windmill vane hand syndrome, and originally described by Freeman and Sheldon,¹ FSS is described as a myopathic distal arthrogryposis. Diagnosis requires the following: microstomia, whistling-face appearance (pursed lips), H-shaped chin dimpling, nasolabial folds, and multiple contractures of the 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, these patients die from respiratory complications during infancy.⁵ Although intelligence is typically normal, certain patients with FSS may exhibit mental retardation, hypotonia and early death⁶ associated with additional missense allelic variations in the sodium leak channel, non-selective.⁷ FSS expression is frequently from new allelic variation.⁸ FSS frequency remains unknown, mostly due to diagnostic uncertainty. There appears to be neither sex nor ethnic preference. Prenatal diagnosis can be achieved via ultrasound or myosin heavy chain 3 (MYH3; MIM *160720) sequencing analysis. Environmental and parental factors are not implicated in the pathogenesis. Potential for MH, and difficult intubation and vascular access, complicate operative planning.

Toydemir *et al*⁹ and Tajsharghi *et al*⁸ show that the basic genetic defect in MYH3, at 17p-13.1, associated with FSS phenotypes, indicates disrupted ATP binding to MYH3. It is unknown how this disrupted binding might correlate to the phenotypes observed,⁹ but it is suggested to influence myophysiology during early development by producing joint contractures due to haploinsufficiency of MYH3's product (embryonic *MyHC*) and posteriorly to downregulation, attenuating of muscle development and leaving residual defects.^{8–10} Muscle cells and myofibrils of two patients with missense allelic variation R672C—a commonly identified allelic variation among patients with FSS causing substitution of *arg672*, 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 Several authors have reported white fibrous tissue within histologically normal muscle fibres and complete replacement of muscle by fibrous tissue.

We believe our report of delayed attempted non-operative correction of multiple hand and wrist contractures in an adult with FSS, may have special relevance for surgeons and therapists in the third world or when working with patients with difficult or refractory contractures not successfully

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addressed in early infancy and early childhood. Unlike many congenital syndromes, which frequently involve life-long impairments, important implications exist for neonatologists, paediatricians and plastic surgeons, 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.

CASE PRESENTATION

The patient had a sporadic and especially severe case of FSS, with history significant for dysphagia, chronic failure-to-thrive, high intelligence, dysphasia, recurrent acute respiratory complications and MH-like syndrome, involving surgical (without triggering agents) and non-surgical situations. The patient had over 20 surgeries on feet, knee, and craniofacial structures, most of them unsuccessful and resulting in deteriorated clinical status. The patient's hands presented with such severe flexion contractures at birth that the palmar surfaces and areas between the phalanges could not be cleaned. By discharge at 21 days after birth, her parents were beginning to be able to use cotton-tipped applicators to clean the hands, and by the age of 6 months, the phalanges were beginning to be less tightly contracted. At around 1 year, the patient was able to pick up objects and hold items in her hands. Consultation with hand surgery and occupational therapy services at two major university referral centres was non-productive, and passive correction achieved by the parents' efforts was not accompanied by strengthening exercises from occupational therapy service, resulting in loss of,

essentially, all correction. The parents felt unguided and unsupported in the care of their child. The patient received no professional therapy until presenting again for hand surgery (ALP) and physiology (RJM) consultations at age 24 years. Before the age of 6 months, the patient had been left-handed; she subsequently became right-handed, using her left hand to passively raise her upper left eyelid (figure 1) due to severe blepharospasm causing visual obstruction; at presentation, the patient could perform all tasks equally well with both hands, except writing and using an eating utensil (right-handed tasks) and using a touchscreen tablet computer (left-handed task).

INVESTIGATIONS

Examination revealed a classic whistling face appearance; a striking lack of facial musculature, resulting in about 80% reduction in plasticity; multiple limb malformations; spinal deformities; and other findings consistent with FSS (figures 2–4), as defined by Stevenson *et al* (2006).² The patient's hands showed little active motion and were symmetrically significant for palmar hyperhidrosis, camptodactyly, ulnar deviation of the radiocarpal and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, flexion contracture at the MCP and PIP joints of all digits, fixed extension of distal interphalangeal joints of digits two-four, radiocarpal joint hyperextension (106° left and 108° right) with minimal active extension (70° left and 40° right), absent flexion creases, medially rotated second digits with 90° PIP contracture, pollex fixed in full adduction in the palm, and congenital overriding of some fingers (figure 3). PIP joints of the third to fifth digits could be actively flexed (left 15°;

Figure 1 Patient at age 2 years responding to parental request to 'smile' by pushing her oral commissures up. Deformities of the hands are clearly visible.

Figure 2 Frontal photograph at the age of 21 years, illustrating classic Freeman-Sheldon syndrome (FSS) craniofacial features.

Figure 3 Lateral view of left (A) and right (B) hand in maximal active extension of interphalangeal joints showing characteristic DA-type features. 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.

right 10°) and could be extended passively (left 95°; right 80°), without discomfort to the patient. Grip strength was relatively well preserved. There was minimal pincer-grasp between the pollex and fifth digit bilaterally.

During passive manipulation, the regional muscle groups did not appear to be contributing to the present status of the hand and wrist contractures; resistance was exclusively in the tendons, ligaments and other connective tissue, suggesting at least secondary syndromic affectation. Radiographic examination demonstrated good joint spacing, without fibrosis, other bony pathological process or any evidence of bone involvement in maintaining or perpetuating the deformities.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for FSS include: Sheldon-Hall syndrome—formerly described as Freeman-Sheldon variant, distal arthrogryposis type 1, distal arthrogryposis type 3 and isolated non-syndromic deformities, but our patient presented with the classic pathognomonic features of FSS of H-shaped chin

Figure 4 Legs and feet showing considerable surgical modification. 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).

dimpling, microstomia, whistling face (pursed lips) appearance and prominent nasolabial folds, excluding the possibility of another diagnosis.²

TREATMENT

After preprocedural consultation and informed consent, the patient was placed seated in an upright position at a 90° angle to the right of the operator, and with patient's left arm pronated, flexed at the elbow, abducted at the glenohumeral joint, and cradled in the operator's supinated right arm and hand. The operator's left (active) hand was positioned on the patient's dorsal hand-wrist complex, with his right (passive) hand providing resistance and protective support extending from the phalanges to glenohumeral joint. Therapy sessions began with application of heat to the forearm, and massage, followed by light passive manipulation and range of motion testing. Following this, increasingly strong dorsolateral force, to reduce hyperextension and ulnar deviation, was applied. Final 10 'maximal' repetitions of equal force were titrated to that point based on operator sensation of a 'stop' in the radiocarpal joint motion, and physiological tensing of palpable tendons and ligaments. Notably, the force required to achieve these end points was very considerable and reached the upper limits of the patient's tolerance. Careful monitoring of the physiological responses of the tendons and ligaments through concomitant palpation of targeted structures with the operator's passive hand was mandatory due to the extremely high levels of force applied; it was felt that this procedure could be particularly dangerous, such that only one operator, an experienced physiologist specialising in muscle, stress response and FSS (RJM), was authorised by the institutional review board to carry out the therapy.

After each session, the correction was held in place by the operator while taping it using woven cotton conforming gauze as underwrap, 2" PowerTape (Andover Healthcare, Inc, Salisbury, Massachusetts, USA) for abducting the pollex, and 4" VetRap Bandaging Tape (3M Healthcare, St Paul, Minnesota, USA) to provide rigidity and avoid compression. Different bracing and taping techniques and products were tried, but this combination was most effective and least bothersome for the patient. The patient was able to remove the taping to shower but had to remain aware of her hand and wrist, and strictly minimise time without the taping, and she was able to dress with the taping in place. Therapy sessions lasted about 30–45 min, including taping. Optimally, it was preferred to have a session daily, skipping 2 days weekly; although, therapy every other day was also effective. Skipping more than 1 day between therapy sessions resulted in reduced efficacy. Building on a method her

Figure 5 Medial views of hand-wrist complexes showing angle reduction of radiocarpal hyperextension of the left hand, following initial therapy session of *Trial 2*.

parents used when she slept as a small child, the patient placed small plush animals in her hand, which was more effective than taping alone. Procedures were identical for *Trial 1* (age 24 years) and *Trial 2* (age 28 years).

OUTCOME AND FOLLOW-UP

After the initial therapy session for both *Trial 1* (age 24 years) and *Trial 2* (age 28 years), there was noticeable angle reduction of the radiocarpal hyperextension (figure 5). Approximately 3 months after initiation of therapy in both *Trial 1* and *Trial 2*, significant and functionally meaningful correction was achieved (figure 6). In *Trial 2*, more therapeutic emphasis was directed toward the pollex, and the patient had gained usable pincer-grasp with the distal aspect of her pollex apposing to the third digit (figure 7). Unfortunately, therapy was interrupted after 3 months in the *Trial 1* and *Trial 2* by severe health problems in the physiologist's family; having achieved good results, the plan is to resume therapy when feasible.

DISCUSSION

FSS is a highly variable syndrome comprising individual genotype-phenotype correlations,¹² about which relatively little

Figure 6 Left hand showing improved extension of all digits, at 3 months after initiation of therapy during *Trial 2*. No therapy was carried out on the right, which is shown for comparison. The improved radiocarpal hyperextension angle of the left is not well appreciated in this view but was considerable, approximately 35°.

Figure 7 Patient demonstrating functional pincer-grasp holding a pocket computer sync cable with the distal aspect of her pollex apposing to the second and third digits, after 3 months of therapy during *Trial 2*.

is known and guidance absent. Experience with our patient suggests that, while best approached in infancy and early childhood, moderate to full functional correction of severe hand contractures may be achievable via non-operative means in the adult patient with FSS, a previously unconsidered approach due to expectation of joint fibrosis. We expect that tendon lengthening procedures may be required, but this is relatively less invasive than attempting complete operative hand and wrist reconstruction. Our patient was willing to accept considerable discomfort during therapy; therefore, we caution that careful patient selection and preprocedural psychological preparation are of paramount importance when foregoing regional anaesthesia and sedation during similar non-operative therapy sessions. We suggest this procedure could be used successfully within this and similar patient populations.

Patient's perspective

- ▶ It was uplifting and very encouraging to see such a change after even the first 'adjustment'!
- ▶ Having so many things simply not work, it was very refreshing to see improvement each time. After only a few weeks, there had been so much change that I had to relearn how to use my hand. I recall just walking around our home in amazement holding a piece of paper between my thumb and finger—something I was doing for the first time in my life! The considerable discomfort during therapy sessions—not pain, per se—I endured, was definitely worth it, and there was no discomfort except during therapy sessions. Knowing what is possible, I look forward to resuming therapy and correcting problems that my hands experience.

Learning points

- ▶ Our experience shows that non-surgical correction should not be abandoned for patients with long-standing hand deformities, provided no bony changes have occurred. Providers should be aware, and patients and family should be cautioned, that improvement will be much slower and more difficult to avoid potential assumption of treatment failure.
- ▶ Early efforts with infants should be focused on supporting parents to perform structured in-home stretching and other exercises to increase functional hand use.
- ▶ When fabricating hand splints, particular attention should be placed on using non-irritating materials and avoidance of possible pressure points.
- ▶ While this experience shows the potential for delayed non-operative hand therapy, early correction is still strongly preferred for optimal developmental, social and physiological functioning.

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Contributors With ALP, RJM was the primary originator and designer of the method described, and both were involved in collection, analysis and interpretation of clinical data. MIP, who primarily drafted the contemporaneous testing report and manuscript, also participated in analysis and interpretation of the findings, along with RLC, who worked on drafting of the manuscript, as well. All critically revised the manuscript for intellectual content and style, but sadly, ALP died very unexpectedly on 30 October 2010.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Freeman EA, Sheldon JH. Cranio-carpo-tarsal dystrophy: undescribed congenital malformation. *Arch Dis Child* 1938;13:277–83.
- 2 McKusick VA. *Online mendelian inheritance in man, OMIM™*. Baltimore: Johns Hopkins University. MIM Number: #193700. Retrieved: 6 May 2015. <http://omim.org>
- 3 Stevenson DA, Carey JC, Palumbos J, *et al.* Clinical characteristics and natural history of Freeman-Sheldon syndrome. *Pediatrics* 2006;117:754–62.
- 4 Al-Haggar M, Yahia S, Damjanovich K, *et al.* p.R672C mutation of MYH3 gene in an Egyptian infant presented with Freeman-Sheldon syndrome. *Indian J Pediatr* 2011;78:103–5.
- 5 Tastekin A, Ikbal M, Ors R. Laryngomalacia, choanal atresia and renal anomaly in a newborn with Freeman-Sheldon syndrome phenotype. *Genet Couns* 2004;15:383–6.
- 6 Zampino G, Conti G, Balducci F, *et al.* Severe form of Freeman-Sheldon syndrome associated with brain anomalies and hearing loss. *Am J Med Genet* 1996;62:293–6.
- 7 Chong JX, McMillin MJ, Shively KM, *et al.*, University of Washington Center for Mendelian Genomics. De novo mutations in NALCN cause a syndrome characterized by congenital contractures of the limbs and face, hypotonia, and developmental delay. *Am J Hum Genet* 2015;96:462–73.
- 8 Tajsharghi H, Kimber E, Kroksmark AK, *et al.* Embryonic myosin heavy-chain mutations cause distal arthrogryposis and developmental myosin myopathy that persists postnatally. *Arch Neurol* 2008;65:1083–90. Erratum: *Arch Neurol* 2008;65(12):1654.
- 9 Toydemir RM, Rutherford A, Whitby FG, *et al.* Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. *Nat Genet* 2006;38:561–5.
- 10 Tajsharghi H, Oldfors A. Myosinopathies: pathology and mechanisms. *Acta Neuropathol* 2013;125:3–18.
- 11 Racca AW, Beck AE, McMillin MJ, *et al.* The embryonic myosin R672C mutation that underlies Freeman-Sheldon syndrome impairs cross-bridge detachment and cycling in adult skeletal muscle. *Hum Mol Genet* 2015;24:3348–58.
- 12 Beck AE, McMillin MJ, Gildersleeve HI, *et al.* Genotype-phenotype relationships in Freeman-Sheldon syndrome. *Am J Med Genet A* 2014;164:2808–13.

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