Case Report

Freeman–Sheldon Syndrome: First Molecularly Confirmed Case from Sub-Saharan Africa

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We report a case of a male baby who has characteristic signs of Freeman–Sheldon syndrome, a rare but recognizable, severe autosomal dominant form of distal arthrogryposis. Diagnosis was based on the distinctive clinical characteristics of the syndrome and confirmed by genetic analysis that showed a de novo missense mutation c.2015G>A (p.Arg672His) of the MYH3 gene.

We highlight the different features present in our patient and describe the etiology of the Freeman–Sheldon phenotype and how its clinical complications can be dealt with. To the best of our knowledge, this is the first molecularly confirmed case of Freeman–Sheldon syndrome in sub-Saharan Africa.

1. Introduction

First reported in 1938 by Freeman and Sheldon who initially called it cranioacetabular dystrophy [1], Freeman–Sheldon syndrome (FSS; OMIM #193700), also known as cranioacetabular dysplasia, windmill vane hand syndrome, distal arthrogryposis type 2A, and whistling-face syndrome, is a rare form of multiple congenital contracture syndrome. It is inherited in an autosomal dominant pattern [2] with most cases occurring sporadically with no family history of the disease. It is characterised by facial and distal limb contractures, the most common being microstomia with pouting lips, camptodactyly with ulnar deviation of the fingers and talipes equinovarus. Facial characteristics comprise micrognathia, microglossia, high arched palate, vertical skin folds in the jaw, H-shaped chin dimple, and a characteristic “mask-like” facies. Other features are dental crowding, strabismus, and hearing loss. Kyphoscoliosis may present later in life. Speech and motor development are delayed; however, cognitive development and life expectancy are usually normal. To date about 100 individuals bearing the characteristic clinical phenotype have been reported [3]. The genetic basis was unravelled in 2006 with missense mutations in the motor domain of the embryonic myosin heavy chain MYH3 gene, which encodes embryonic myosin, one of the proteins of the contractile complex of skeletal muscle cells [4].

In the African continent, FSS has already been reported in Tanzania [5], South Africa [6], and Egypt [7]. To the best of our knowledge, we hereby describe the first molecularly confirmed FSS patient from sub-Saharan Africa, in whom MYH3 mutation analysis revealed a recurrent pathogenic missense mutation.

2. Case Report

A newborn male was shortly after birth referred to our hospital. He was brought in by the mother with a main complaint of abnormal facial, genital, upper, and lower limb features since birth. He was born at term with a gestational age of 39 weeks by spontaneous vaginal delivery, a birth weight of 3.1 kg, and an APGAR score of 5 and 7 in the 1st and 5th minute, respectively. He is the 4th child born to healthy and nonconsanguineous parents. All other children are alive and developing well and none have congenital abnormalities. Currently, the mother is 36 years old and the father is 45 years old. The mother consumed alcohol about once or twice a month during pregnancy, never excessive. Pedigree analysis showed that none of the other family members had the same anomalies.
Figure 1: (a) from left to right shows micrognathia and low-set crumpled ears, camptodactyly of the right hand, and camptodactyly and "windmill vane position" of the left hand. (b) from left to right shows congenital vertical talus of the right foot (rocker bottom foot), Talipes equinovarus of the left foot (club foot) and chordee. (c) shows the "mask-like" face with a wide and flat nasal bridge, ocular hypertelorism, microstomia, and puckered lips ("whistling face").

Based on the history and physical examination, the clinical diagnosis was FSS. Venous blood was sampled and sent to the Genome Diagnostics Nijmegen of Radboud University Medical Center, Nijmegen, Netherlands, for confirmation of the clinical diagnosis.

DNA sequence analysis of the $MYH3$ gene revealed a heterozygous missense mutation c.2015G>A (p.Arg672His), which was absent in both parents. This mutation is pathogenic because it is de novo, has been published already [4], and was not observed in the exomes of more than 60000 presumably healthy individuals according to the ExAc browser (http://exac.broadinstitute.org).

3. Discussion

Distal arthrogryposis (DA) is an inherited primary malformation involving multiple congenital contractures of the upper and lower limbs, for example, camptodactyly, absent/hypoplastic flexion creases, overriding fingers, talipes equinovarus, calcaneovalgus deformities, and vertical talus. Nine groups have been classified by Bamshad et al., each one numerically labelled in order of similarity to DA1 which was
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which included the presence of two or more of the clinical

manifestations of DA described above plus the presence of a

small pinched mouth, prominent nasolabial folds and H-

shaped dimpling of the chin [4, 9]. In contrast to FSS, there is genetic heterogeneity in SHS in which, apart

from MYH3 mutations, there are also mutations observed in

TNNI2, TNNT3, and TPM2 [9, 10]. In 2006 strict clinical
criteria for classical FSS were published by Stevenson et al.

which included the presence of two or more of the clinical

manifestations of DA described above plus the presence of a

small pinched mouth, prominent nasolabial folds and H-

shaped dimpling of the chin [11]. Since all these criteria were

apparent in our patient, it was not very difficult to reach a

provisional diagnosis. However, there is a broad spectrum of

variability in the clinical presentation of FSS to the extent that

only orofacial manifestations of the disease can be present

without abnormalities of the limbs [12]; thus genetic analysis

is often needed to reinforce the diagnosis.

FSS is caused by a mutation of the embryonic myosin

heavy chain MYH3 gene, which is present on the short arm of

chromosome 17. MYH3 protein aids in the production of the

skeletal muscle cells which is vital for normal development

of muscles before birth. MYH3 expression has been seen to

be downregulated in skeletal muscle when nearing the end

of gestation in humans [13], suggesting that the contractures

are not progressive after birth and will not influence con-

tractile function postnatally. However, a more recent study

has shown conflicting results [14]. Genetic analysis of our

patient revealed the most common mutation found in FSS

which is the heterozygous missense mutation c.2015G→A

(p.Arg672His), which accounts for around 45% of MYH3

mutations in FSS.

A genotype-phenotype correlation study revealed that by

using a severity score system (ranging from 0 to 37) that takes

into account the physical findings of the upper and lower

limbs and face, as well as the natural history of DA [15], the

pThr178Ile mutation gives the most severe phenotype and the

p.Arg672Cys mutation the least severe phenotype, while the

p.Arg672His mutation shows intermediate severity. Together

these 3 mutations account for more than 90% of the MYH3

mutations in FSS [16]. Beck et al. found that the severity scores

of patients with the p.Arg672His mutation ranged from 4 to

15 with a mean of 9.2. Most of the clinical variability appeared

to be in the lower limb features [16].

Mutations can either occur sporadically in every first case

of FSS in a family—as in our case—or it can be passed on from

one generation to the next as an autosomal dominant trait [2]

with a 50 percent chance to pass it on to the offspring. Occur-

rences of FSS in sibships with normal parents (but without

molecular confirmation) suggests an autosomal recessive pat-

tern [17–19] and, with 2 affected brothers, X-linked recessive

inheritance has also been reported [20]. Recently, mosaicism

in a phenotypically normal parent of a girl with FSS has been

observed [21]. As already suggested by Stevenson et al. [11],

these cases could well have been due to parental mosaicism.

MYH3 mutations are not exclusive to FSS alone. These have

also been found in SHS (DA2B) [4] and multiple pterygium

syndrome (DA8) [22] and quite recently in autosomal domi-
nant spondylocarpotarsal synostosis syndrome [23].

Obviously, management of such a complex disorder as

FSS requires a multidisciplinary approach, starting from

birth. Because of the characteristic orofacial manifestations

like microstomia (pouting lips), microglossia, and microg-
nathia, many newborns with FSS experience feeding difficul-
ties due to the inability to form a tight seal around the nipple.

Exclusive breast feeding rarely works; hence alternatives like

using specialized bottle-top nipples, orogastric or nasogastric

tubes, gastrostomy tubes, or expressing breast milk and feed-
ing the baby using either a small container or spoon have been

used for the first months of life or even longer. Regardless of

the method used, commissurotomy has shown improvement

in the ability to feed [11]. Bilateral commissurotomy followed

by the use of a patient customized dynamic oral commissure

retractor has been effective in dealing with microstomia and

preventing recurrence due to scar contracture that occurs

months following surgical intervention [24].

Distal limb contractures should be dealt with by early

physiotherapy where manipulative techniques such as the

Ponseti method can be used for talipes equinovarus. In case of

refractory early intervention, surgical correction can also be

employed. Unlike talipes equinovarus, vertical talus rarely

responds to stretching and casting alone; however, a com-
bination of early serial manipulations and casting followed

by limited surgical correction by tenotomy and k-wires has

shown to be successful [25].

Patients with FSS require numerous hospital admissions

and surgeries throughout life averaging 17 and 10.3 per indi-

vidual, respectively [11]. The aim of these surgeries is to try to

correct the phenotypical manifestations. Some of these sur-
geries are most effectively performed at particular age groups,

for example, commissurotomy should be done earlier to over-
come feeding difficulties and speech delays whereas correc-
tive surgical procedures for limbs can be done later, once con-
servative management has failed. Therefore, counselling par-
ents/guardians regarding all these management issues is of

paramount importance.

Numerous complications can occur during surgery on

patients with FSS. The most common is difficult intubation

[26, 27], secondary to the microstomia, high arched palate,

and micrognathia which does not improve with neuromuscu-

lar blockade or general anaesthesia [28]. The uses of a laryn-
geal mask airway [29] for short procedures and fibre-optic

bronchoscopy [30] have both been successful in the difficult

airway management of these patients. Another complication

observed multiple times in patients with FSS is malignant

hyperthermia [26, 31] with a frequency of 16% as reported by

Stevenson et al. [11]. It normally develops with use of volatile

anaesthetics, for example, in halothane induction with or

without the use of muscle relaxants like succinylcholine. It

is a condition in which muscles enter a hypermetabolic state

resulting in elevated temperature as a consequence of heat
production, increased heart rate, acidic breathing, muscle rigidity, and rhabdomyolysis which can lead to acute kidney injury and eventually to multiple organ dysfunction syndrome and death, if not treated aggressively. Hence, when surgery is considered, volatile anaesthetics and depolarizing muscle relaxants should be avoided and it should be done at facilities that are geared to deal with these complications, should they arise.

In conclusion, FSS is a rare but recognizable, generally severe, autosomal dominant type of DA, due to mutations in the MYH3 gene. We described the first FSS patient from sub-Saharan Africa, in whom a MYH3 mutation was found. Patients with FSS should be evaluated and managed from birth by healthcare professionals from multiple fields of medicine including paediatricians, dentists, anaesthesiologists, orthopaedic and craniofacial surgeons, physiotherapists, and occupational therapists in order to gauge the severity of their phenotypical presentation and create an appropriate personalized management plan.

Conflicts of Interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References


