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 craniocarpotarsal dystrophy [1], Freeman–Sheldon syndrome (FSS; OMIM #193700), also known as craniocarpal-tarsal 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”).

On inspection, an active newborn was seen with a normal level of consciousness and pink in room air. He was hypothermic (33.5°C) and tachypneic (77 bpm) with an appropriate heart rate for the age (147 bpm). As shown in Figure 1, he had multiple craniofacial abnormalities including micrognathia and low-set ears, a wide and flat nasal bridge, ocular hypertelorism, squinted eyes, microstomia, and puckered lips that looked like as if he was whistling. Multiple contractures including camptodactyly of both hands with fingers in the “windmill vane position,” a right congenital vertical talus, and left talipes equinovarus were noted. On genitourinary examination, chordee (downward curved penis) was seen without hypospadias. Initially, expressed breast milk was given through a nasogastric tube. Additional investigations such as brain and cardiac ultrasound were ordered; however they could not be performed due to financial constraints of the mother. Later, the mother was taught how to feed the baby through a container using expressed breast milk and counselled to initiate correction of the talipes equinovarus using the Ponseti method. The child was discharged on day 10 and followed up at the Departments of Physiotherapy and Paediatrics.

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
taken as the model disorder; that is, DA2 is more similar to DA1 than is DA9 [8]. In addition to the congenital contrac-
tures of the upper and lower limbs each DA has distinguishing
characteristic features unique to that form of DA.

FSS (DA2A) is the most severe form of the distal arthro-
gryposes while Sheldon–Hall syndrome (SHS, DA2B) is the
most common. There is a significant phenotypical overlap
between SHS and FSS often causing misdiagnoses between
the two, particularly in children. While both FSS and SHS
have orofacial manifestations, SHS is lacking a whistling face
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
p.Thr178Ile 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-
rances 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, acidotic 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


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