CASE REPORT

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A Case Report of Freeman-Sheldon Syndrome with Gastrointestinal Dysmotility in a Premature Newborn Delivered Due to Polyhydramnios

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ABSTRACT There is no reported case dealing with the relationship of polyhydramniosis and possible gastrointestinal dysmotility in fetuses with Freeman-Sheldon syndrome (FSS). A case report and literature review of FSS with gastrointestinal dysmotility in a premature newborn delivered due to polyhydramnios was presented. A male baby was born from a 24-year-old mother at 30 weeks of gestation due to polyhydramnios through an emergency cesarean section at a birth weight of 1,460 g. The diagnosis of FSS was considered with the clinical findings. It was also confirmed with the genetic screening, that is revealed a heterozygous likely pathogenic variant in the MYH3 gene. In dealing with FSS fetuses and newborns, perinatologists and neonatologists need to pay attention to the possibility of polyhydramnios due to impaired gastrointestinal motility in addition to other congenital malformations and continuing neonatal problems developed under the influence of gastrointestinal dysmotility.

Keywords: Neonate; Freeman-Sheldon syndrome; premature; polyhydramnios; reflux

Freeman-Sheldon syndrome (FSS) was first described in 1938 by Freeman-Sheldon, and more than 100 cases have been described in the literature.[1] Burian et al. rediscovered the entity and called it the Whistling Face syndrome.[2] This syndrome is characterized by multiple contractures at birth, abnormalities of the head, face, hands, feet, and skeletal malformations. In FSS, there could be microstomia, micrognathia, microglossia, "H" or "V" shaped scar-like appearance extending from the lower, shrunken mouth, whistling facial appearance on the face, a long and wide philtrum, hypertelorism, strabismus, ptosis, bilateral blepharospasm, ulnar deviation, flexion in the fingers, and/or having breathing problem.[1,2]

The diagnosis of FSS in a fetus with a positive family history can be made by ultrasonography after 20 weeks of gestation.[3] Polyhydramnios and decreased fetal movements are reported.[4] There is no reported case mentioned about the relationship between polyhydramniosis and possible gastrointestinal dysmotility in fetuses with FSS. A case report and literature review of FSS with gastrointestinal dysmotility in a premature newborn delivered due to polyhydramnios was presented.

CASE REPORT

A male newborn was born from a 24-year-old mother at 30 weeks of gestation due to polyhydramnios through an emergency cesarean section with a birth weight of 1,460 g. The mother had no follow-up records in our hospital. The newborn was admitted to the neonatal intensive care unit with the diagnosis of respiratory distress in the delivery room. There was third-degree consanguinity (cousins). The newborn

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had a healthy brother. On the physical examination, he had a whistling facial appearance, microstomia, micro-retrognathia, long philtrum, low set ears, strabismus, short columella, lower and upper extremity contractures, supination, and pronation restriction (Figure 1). The testicles could not be palpated in the scrotum and a bilateral inguinal hernia was observed. Talipes equinovarus was presented in both lower extremities. Respiratory support treatment was given to the patient with gasping and tachypnea. Appropriate antibiotherapy was initiated. Because the patient was syndromic, the following departments were consulted; medical genetics, orthopedics, ophthalmology, and pediatric surgery. A diagnosis of FSS syndrome was considered with the clinical findings. During the follow-up, the patient had vomiting attacks due to gastroesophageal reflux. The genetic screening revealed a heterozygous likely pathogenic variant in the embryonic myosin heavy chain (*MYH3)* gene of the patient and the diagnosis of FSS was confirmed. The patient was discharged at postnatal 2 months. On the 3rd postnatal month, an operation for the undescended testicle and inguinal hernia was performed by the pediatric surgery department. An achilloplasty operation was performed by orthopedics on the 8th month, under general anesthesia.

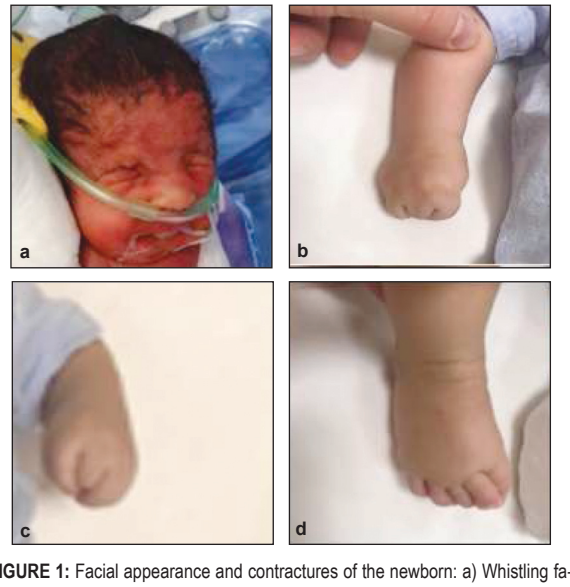

FIGURE 1: Facial appearance and contractures of the newborn: a) Whistling facial appearance, microstomia, micro-retrognathia, long philtrum, low set ears, lower and upper extremity contractures. b,c,d) There are contractures in both hands, and ulnar deviation, and camptodactyly in the third and fourth fingers.

No malignant hyperthermia complications were observed.

Since our study was a case report, ethics committee approval was not required. The permission to use the patient data was obtained at hospital admission.

DISCUSSION

After first described in 1938, FSS was redefined by Burian et al. in 1963 and called the "Whistling Face syndrome".[2] The characteristics of the syndrome, skeletal malformations, and related facial features have been described. Basic skeletal malformations are multiple joint contractures with campodactyly, ulnar deviation of the fingers, equinovarus, and kyphoscoliosis.[5] In these cases, the following has been reported; a flat face, high palate, micrognathia, microglossia, long and wide philtrum, hypertelorism, strabismus, and ptosis, low-set ears, hearing loss, cryptorchidism, and scoliosis.[1-3] FSS syndrome and affected systems and clinical findings were shown in Table 1. Our case had facial anomalies defined in this syndrome along with a typical facial appearance, especially when he was crying. So, the newborn presented the majority of the findings described in the literature.

Difficulty in breathing and swallowing has been described in these newborns at birth. Upper airway stenosis that was severe enough to require tracheostomy has been reported in the FSS cases.[5] Schefels et al. emphasized that respiratory distress is progressive in these newborns, especially up to 2 months. He also reported that patients may require tracheostomy due to progressive respiratory distress.[6] Robinson et al. reported that tracheostomy was performed in one patient who underwent repeated intubation due to upper airway obstruction.[7] Similarly, Altuncu et al. reported that the patient who was diagnosed with FSS with typical facial appearance, extremity contractures, and respiratory distress since birth, died at the age of 2 months due to difficult intubation and recurrent aspiration pneumonia due to upper airway obstruction.[8]

To our knowledge, in the literature, there was only one case with polyhydramnios and decreased

TABLE 1: Clinical manifestations of Freeman-Sheldon syndrome.

Affected systems	Clinical findings	References
Cranio, facial	Microstomia, micro-retrognathia, long philtrum, low set ears, hypertelorism, deep-set eyes, outside corners of the eyes that point downward (down-slanting palpebral fissures), a narrowing of the eye-opening, ptosis, and eyes that do not look in the same direction (strabismus), dental crowding, high narrow palate, prominent supraorbital ridge, telecanthus, short nose, colobomata of the nostrils; weak physiognomical expression; "whistling face"	1-3,10
The respiratory system	Upper airway obstruction, pneumonia, bronchitis	8
Skeletal system	Myopathy, lower and upper extremity contractures, arthrogryposis, camptodactyly, scoliosis, clubfoot, malignant hyperthermia	9
Gastrointestinal system	Polyhydramnios, gastrointestinal dysmotility, feeding difficulties, dysphagia, failure to thrive, growth deficit	4,10
Neurological system	Psychomotor development delay, speech delay	10
Genital system	Cryptorchidism	1-3
Genetic mutation	Autosomal dominant, autosomal recessive MYH3 gene (17p13.1)	9,11

MYH3: Embryonic skeletal muscle myosin heavy chain 3

fetal movements in a newborn with FSS.[4] In this reported case, amnio-drainage was applied twice at 28 and 32 weeks of gestation due to symptomatic polyhydramnios. Our patient also had polyhydramnios. We speculated that the polyhydramnios may be related to gastrointestinal dysmotility because the case had vomiting attacks due to gastroesophageal reflux after delivery. The neonatal problems caused by poor sucking-swallowing function may be also the background of polyhydramniosis and related fetal findings. On the other, we think that polyhydramnios may also cause premature birth as a part of this syndrome. So, in cases with multipl congenital anomalies and polyhydramnios in fetal ultrasonography, FSS should be considered in the differential diagnosis. Vimercati et al. made the diagnosis of FSS in a baby by using ultrasonography according to the nomogram chart prepared by measuring the fetal mouth in a pregnant woman without a family history.

Besides, the mutation in the *MYH3* gene encoded in the 17p13.1 region in FSS, has been reported to cause the disease, and the *MYH3* protein complex is important for the development of muscles before birth.[9] Although the syndrome is inherited as autosomal dominant or autosomal recessive, its clinical findings vary from very mild to severe form due to lack of penetrance and difference in expression among individuals.[1] Most of the reported cases are inherited by autosomal dominant inheritance.[10] In our case, the diagnosis of FSS was confirmed by detecting a known pathogenic heterozygous missense mutation in the *MYH3* gene (c.2015G>A), the variant was not detected in the parents of the patient. So, the case was evaluated as a sporadic case. This variant is associated with a moderate phenotypic appearance and it has been shown that the amino acid substitutions in this codon may be related up to 72% of patients with FSS.[11]

Because of the wide clinical variety in FSS, it should be considered the differential diagnosis of arthrogryposis syndromes, such as distal arthrogryposis (1A, 1B, 2B, 3, 7, 8), Schwartz-Jampel syndrome, and non-syndromic contractures.[12] Accordingly, physical findings, family history, and genetic analysis are helpful in the diagnosis.

FSS is a rarely seen disease related to complex anomalies, and an inheritance pattern cannot be fully revealed. Specific craniofacial anomalies, polyhydramnios, and contractures have been described in fetal ultrasonography. These newborns have sucking and swallowing dysfunction, require considerable nutrition support, surgical treatment, physical therapy, and rehabilitation. As presented above, FSS newborns need to be delivered because polyhydramnios resulted in inevitable premature delivery. The development of polyhydramnios may be due to impaired gastrointestinal motility by a decrease in swallowing and gas-

trointestinal transit time. In dealing with FSS fetuses and newborns, perinatologists and neonatologists need to pay attention to the possibility of polyhydramnios in addition to other congenital malformations and following neonatal problems developed under the influence of disordered gastrointestinal motility.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Fatih Kılıçbay, Gaffari Tunç;* ***Design:*** *Hande Küçük Kurtulgan, Yeşim Sıdar Duman;* ***Control/Supervision:*** *Hande Küçük Kurtulgan, Gaffari Tunç;* ***Data Collection and/or Processing:*** *Fatih Kılıçbay, Gaffari Tunç;* ***Analysis and/or Interpretation:*** *Hande Küçük Kurtulgan, Yeşim Sıdar Duman;* ***Literature Review:*** *Fatih Kılıçbay, Gaffari Tunç;* ***Writing the Article:*** *Fatih Kılıçbay, Gaffari Tunç, Hande Küçük Kurtulgan;* ***Critical Review:*** *Hande Küçük Kurtulgan, Yeşim Sıdar Duman;* ***References and Fundings:*** *Fatih Kılıçbay, Gaffari Tunç.*

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