

Freeman-Sheldon syndrome - a course of the disease from birth to adulthood

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Summary

Freeman-Sheldon syndrome, also known as Whistling Face syndrome, is a rare disorder associated with multiple congenital contractures. In this report, we present the course of the disease from the neonatal period to adulthood in one female patient and discuss the gynecological abnormalities and other medical problems that were encountered.

Key words: Freeman-Sheldon syndrome; Whistling Face syndrome; Arthrogryposis; Multiple congenital contractures.

Introduction

Freeman-Sheldon syndrome (FSS) was first described in 1938 by doctors Freeman and Sheldon as cranio-carpotarsal dysplasia. It is a condition that primarily affects face, hands, and feet [1-4]. The first two children in whom the disorder was diagnosed had microstomia, facial bone flattening, hypertelorism, small nose and nostrils, finger contractures, ulnar deviation of the hands, and bilateral talipes equinovarus [3]. Burian *et al.* rediscovered the pathology and called it Whistling Face syndrome due to the fact that microstomia and a scar-like mark extending from the lower lip to the bottom of the chin cause the infants to appear as if they were attempting to whistle [5]. Bamshad *et al.* classified Freeman-Sheldon syndrome as a form of distal arthrogryposis with facial abnormality and suggested that it should be called distal arthrogryposis type 2A (DA2A) [6].

Freeman-Sheldon syndrome is a rare disorder that affects males and females in equal numbers. Its exact prevalence is unknown [2]. Approximately 100 cases have been reported in the literature so far [1]. It belongs to a group of disorders that are associated with multiple congenital contractures (MCCs), which occur in approximately 1 in 3,000 children. Since the disease shares traits with other MCCs, it is sometimes misdiagnosed, and it is difficult to determine its actual frequency in the general population [1]. It should be differentiated from other arthrogryposis syndromes, Schwartz-Jampel syndrome, and trismus-pseudocamptodactyly syndrome (TPS) [6, 7]. It is the most severe form of distal arthrogryposis [2]. The most important clinical manifestations typical for Freeman-Sheldon syndrome are listed in Table 1.

This report describes a patient with Freeman-Sheldon syndrome. We present the course of the disease from the

neonatal period to adulthood and discuss the medical problems that were encountered. The analysis was performed retrospectively basing on the medical records of the patient. We obtained the patient's informed consent for publication of the data.

Case Report

The female baby was born in a regional hospital, at term, by emergency cesarean section because of fetal distress and risk of perinatal hypoxia. The patient's mother was 35 years old, previously healthy. It was her 4th pregnancy and delivery. The pregnancy had been uneventful, and there was no history of congenital abnormalities in the immediate family. The infant's birth weight was 3,050 g, and the Apgar scores were 8 at 1 minute and 9 at 5 and 10 minutes. Several anatomical abnormalities were noted immediately after birth, particularly contractures of the major joints in the lower limbs and a tiny mouth that could not be fully opened.

In the first days of life, feeding problems developed, including difficulty in sucking and swallowing, as well as choking. Basing on the chest X-ray and gastroesophageal scintigraphy, trachea-esophageal fistula, and gastroesophageal reflux were excluded. Gradually, the sucking reflex developed and the infant was fed by teat with baby formula milk. Laryngomalacia, with stridulous breathing and profuse salivation, were observed from birth and caused problems for several years. On cardiological examination, patent ductus arteriosus and foramen ovale were diagnosed. No pathology was observed in the cranial and abdominal ultrasound exam.

The baby was consulted by an orthopedist who diagnosed her with arthrogryposis, left cleft foot (pes escinovarus), and right flatfoot (pes planovalgus). Bilateral hip dysplasia was also observed. At the age of one, the child

Table 1. — *Clinical manifestations of Freeman-Sheldon syndrome [1, 4, 7].*

Freeman-Sheldon Syndrome – Clinical manifestations
Congenital contractures of hands and feet (fingers, wrists, ankles) – camptodactyly with ulnar deviation of the hand, talipes equinovarus
Proximal joint involvement (hips, elbows, knees); joint dislocations
Microstomia with pouting lips
Characteristic face – prominent supraorbital ridge, sunken eyes, telecanthus, short nose, colobomata of the nostrils; weak physiological expression; “whistling face”
Scoliosis
High narrow palate
Dental crowding
Feeding difficulties, dysphagia, failure to thrive, growth deficit
Life-threatening respiratory complications and severe respiratory infections
Psychomotor development delay, speech delay

underwent the first feet surgery. Another correction of the right foot was performed at the age of 4 and of the left foot at the age of 6. Psychomotor development was slightly retarded. She started to sit at the age of 6 months but settling into a standing position, and the first steps were delayed due to feet deformations. At the age of 5, the child was moving independently on a slightly expanded basis. Locomotion improved after feet corrections.

The chromosome analysis revealed a normal female karyotype with an increase in the length of the satellite on the short arm of chromosomes 15 and 21. On consultation, the geneticist suggested dystrophia cranio-carpotarsalis, which is another name for Freeman-Sheldon syndrome. Additional genetic tests were not performed. The final diagnosis was based on the medical history and physical examination.

In the first months of life, the patient was floppy. She was consulted by a neurologist, and several functional examinations were performed. The results of motor and sensory nerve conductions, as well as electromyography, were within a normal range, which excludes peripheral neuropathy, demyelination process, disorders of the neuromuscular junction and of the muscles. Deep reflexes and plantar response were also normal, which rules out upper motor neuron lesion. At the age of 8, the patient was referred for neurologic consultation and imaging examination because of an episode of convulsions. On EEG ictal discharges of high voltage, theta waves were observed. CT scanning revealed thickened grey matter in the parietal lobes, and polymicrogyria or grey matter heterotopy were suspected. This structural abnormality was probably the reason for the earlier observed hypotony and convulsions.

Speech understanding was adequate during development; however, she could hardly speak until she was five years old. At the age of 8, she was consulted by a speech therapist who identified a high-arched palate, crowding in both arches and malocclusion, as well as significantly weakened motor skills of the tongue and circumoral muscles. He also observed problems with phonemic hearing

and minimal vocabulary.

Eating problems were observed for many years. The patient could not swallow in the sitting position due to choking; the reclining position was more comfortable. At the age of two, she could only eat pulpy food and was still salivating profusely. Salivating diminished gradually, and feedings were better tolerated with time. In childhood, the patient was consulted several times by an orthodontist because of difficulty in opening the mouth. At the age of 7, the maximal jaws dilation was 1.5 cm, and temporomandibular joint dysfunction was suspected. On further examination, no bony ankylosis was diagnosed, and the patient was not qualified for surgical treatment. Orthodontic management with jaws dilation and rehabilitation were continued. At the age of 14, the patient was consulted by an esthetic surgeon because of microstomia and was not qualified for surgery either. Most of the dental treatment required general anesthesia because of difficulty in opening the mouth.

At the age of 18, the patient was diagnosed with hypertrophy and hyperpigmentation of labia minora. She suffered from discomfort, pain, and physical activity limitation due to this condition. She reported regular menstrual cycles since menarche at the age of 14. Symptoms of hormonal disturbances and other chronic diseases were not observed. At the physical examination, the development of sex characteristics was adequate to the age - according to Tanner's scale: P4, A4, Th4. Gynecological examination revealed labia minora hypertrophy (8 cm length between the base and the wedge), petite vagina, and a small opening in the hymen. The uterus and adnexa were normal in transrectal palpation. Transrectal ultrasound showed typical uterus and ovaries. Hormonal tests (folliculotropin, lutropin, prolactin, thyreotropin, total testosterone, and sex hormone binding globulin) were in the normal ranges. The patient was informed about the possibility of the labioplasty procedure and accepted the proposal of surgical treatment. The labial reduction was performed by wedge resection of labia adjusting the size to the desired one (2 cm length between the base and the wedge). Three weeks and six months after

surgery, the patient reported full acceptance of her genital anatomy. She did not mention hyperpigmentation of the labia anymore and reported successful sexual life with her boyfriend.

At present, the patient is 25 years old. In general, she is in good mood and health. She moves with little difficulty. The contact with the patient is good; she answers logically to questions. Speaking is difficult for her, but the speech is understandable. She also reports problems with swallowing. The patient got married to a disabled man. They do not plan to have children, so she receives a contraceptive injection every three months. She did not get any job and is not employed gainfully but can do the housework.

Discussion

Freeman-Sheldon syndrome belongs to a group of disorders that occur with multiple congenital contractures. A congenital contracture is a structural deformity that hinders normal flexion and/or extension of a specific area of the body [2]. Arthrogryposis is diagnosed when contractures are present in one or more regions of the newborn's body. According to the criteria of FSS, the syndrome can be diagnosed based on the medical history and physical examination that reveal characteristic dysmorphic status combining bone anomalies and joint contractures with typical facies features [7]. The features observed in our patient that allowed for the diagnosis of FSS are: congenital contractures of hands and feet, the involvement of the proximal joints (mainly hips), characteristic facial traces, microstomia, and oral contractures causing severe feeding difficulties at birth, dental crowding and speech delay. Although genetic confirmation may be preferable in diagnosing FSS, genetic testing is not always available. This is especially true in the case of stringent ethical regulation and also considering the patient's or parents' wish. Thus, diagnosis based on clinical findings is critical.

In most patients, Freeman-Sheldon syndrome occurs randomly, with no apparent cause (sporadically). In some of them, mutations in the embryonic myosin heavy chain (*MYH3*) gene located on the short arm of chromosome 17 (17p13.1) have been detected [7-9]. Other cases are inherited as an autosomal dominant trait [1]. In some rare cases, clinically indistinguishable from Freeman-Sheldon syndrome, an autosomal recessive or X-linked recessive inheritance has been suggested, as parents of the individuals with the disorder have been closely related (consanguineous) [1]. In the case of our patient, it has been concluded that the syndrome occurred randomly, so the risk for the parents of having the next baby with the same disease was very low, about 1%. On the contrary, the risk of Freeman-Sheldon syndrome in the offspring of the patient is significantly increased, within the range of 25%-50%, considering the possibility of an autosomal recessive or autosomal dominant inheritance [1, 7]. An accurate risk assessment can only be made when mutation analysis is performed. Unfortunately, our patient has not approved such

an examination.

Nowadays, prenatal diagnosis is possible by ultrasound scan, where facial and limb abnormalities can be detected in the second-trimester anomaly scan [7, 8, 10]. A standard chart for fetal lip width prepared by Vimercati *et al.* can be used if microstomia is suspected [10].

Problems with feeding, which were observed in the first years of life of our patient, are typical for Freeman-Sheldon syndrome, as various abnormalities of the head and face are among the principal manifestations of this disorder. Affected infants have an unusually puckered mouth (microstomia) and a raised scar-like mark in the shape of an "H" or a "Y" extending from the lower lip to the bottom of the chin due to contractures of circumoral muscles [2, 4]. These traits cause the infants to appear as if they were attempting to whistle [1, 3, 5, 8]. They usually also have a flat middle portion of the face, a "masking" or immobile facial appearance, full cheeks, a high roof of the palate, micrognathia, malocclusion, abnormal crowding of the teeth, and/or microglossia. Malformations of the mouth and jaw may cause diminished ability to suck, speech abnormalities, difficulty in swallowing, and eating [4]. These problems often result in a failure to grow and gain weight at the expected rate [1].

Respiratory problems that may occasionally lead to life-threatening complications are also observed in patients with Freeman-Sheldon syndrome [8, 11, 12]. Some children require tracheostomy due to stridulous breathing [11, 12]. Besides, swallowing and feeding difficulties may cause foreign material to be aspirated into the lungs, which sometimes results in severe aspiration pneumonia [1, 8]. Affected children may also have nasal speech due to limited movement of the soft palate [1]. The patient presented in this report did not have severe respiratory problems. Stridor and tracheomalacia were observed in the first years of life but resolved with time. However, she had issues with speaking for a long time due to limited mobility of the tongue and facial muscles, as well as microstomia and high roof palate.

Some findings associated with Freeman-Sheldon syndrome suggest the disorder may be a form of muscle disease known as myopathic arthrogryposis, a condition in which an underlying pathology of the muscles results in permanent fixation of the joints of the fingers and toes [1]. Feeding difficulties may also be connected with the increased muscle tone [8].

Patients with FSS usually require consultations with craniofacial and orthopedic surgeons because of craniofacial, feet, and hands deformities and contractures that restrict movements [1, 2]. Patients typically have multiple contractions in the hands and feet that cause camptodactyly, a hand deformity ("windmill vane hand"), and clubfoot. They can also have scoliosis. However, surgery should be pursued cautiously, with avoidance of radical measures and careful consideration of the abnormal muscle physiology. Many surgical procedures have suboptimal outcomes due to coexisting myopathy [2]. The patient described in our re-

port had several surgeries for feet deformations. They were undertaken in early childhood so that the developmental delay could be minimized. The locomotory progress of the patient was delayed, but at the age of 5, she could move without significant problems. The patient was also consulted several times by an orthodontist and esthetic surgeon due to microstomy and difficulty in opening the mouth. However, surgical intervention was not undertaken, and conservative treatment and rehabilitation were continued until the results were satisfactory.

People with Freeman-Sheldon syndrome may develop a severe reaction in the form of malignant hyperthermia to certain drugs such as muscle relaxants, and anesthetic gases during surgery. The symptoms are muscle rigidity, rhabdomyolysis, high fever, acidosis, and tachycardia. It can be life-threatening, so all surgical interventions with general anesthesia should be planned carefully, and both patients and doctors should be aware of the risk [2, 13]. The additional problem might be a difficulty with tracheal intubation via direct laryngoscopy due to a tiny mouth opening [2, 12, 13]. Robinson reported a case of a patient with Freeman-Sheldon syndrome and upper airway obstruction who required tracheostomy in the neonatal period [12]. There is also a report of a patient with difficulties during intubation because of cervical kyphoscoliosis [14]. The patient presented in our report did not demonstrate any complications during surgeries. She had many procedures with general anesthesia performed, including orthopaedical and gynecological surgery, as well as dental treatment.

Intelligence and life expectancy are average in the majority of patients with FSS. There are occasional reports of association with mental retardation or some degree of intellectual disability [2]. However, modest motor and speech delays are observed in childhood [8]. These problems were also encountered by our patient who developed normal locomotion much later than other children. She also had difficulties with speech development and required long orthodontic treatment and worked with a speech therapist for many years.

Affected patients may have many abnormalities in the eyes, such as hypertelorism, deep-set eyes, down-slanting palpebral fissures, narrowing of the eye-opening, ptosis, and strabismus [2]. We did not observe any of these abnormalities in our patient.

Zampino *et al.* suggested that it would be more appropriate to talk about Freeman-Sheldon spectrum rather than syndrome because of different pathogenetic mechanisms, the wide range of clinical manifestations, and the genetic heterogeneity [15]. They described a patient with traits typical for Freeman-Sheldon syndrome in whom cerebellar and brainstem atrophy was diagnosed, and hearing loss was observed. They suggested that in most severe forms of FSS, brain abnormalities may be responsible for some clinical manifestations, i.e., respiratory problems, difficulty in swallowing, and hypertonicity [15]. The patient presented in the report was consulted by a neurologist due to

the episode of convulsions in childhood. Imaging studies such as CT and MRI scanning revealed polymicrogyria and heterotopy of the grey matter. In some papers, such abnormalities were presented as connected with different forms of arthrogryposis [16, 17].

The patient presented in our paper reconfirmed the known clinical characteristics of Freeman-Sheldon syndrome. A variety of clinical manifestations was observed in a single person based on a detailed long-term observation. Additionally, this is, to our knowledge, the first report of a patient with Freeman-Sheldon syndrome and labia minora hypertrophy. The gynecological aspect was described in detail in our previous paper [18]. So far, no embryological connection between the labia minora overgrowth and Freeman-Sheldon syndrome was reported. Labioplasty in FSS patient with labia minora hypertrophy can help to obtain both the full acceptance of genital anatomy and successful sexual life.

Ethics Approval and Consent to Participate

The patient gave her consent for information about herself to be described in the paper. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Poznan University of Medical Sciences.

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Conflict of Interest

The authors declare no conflict of interest.

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