CASE REPORT

Recessive type of Freeman-Sheldon syndrome
- report of two affected siblings

Gerson Carakushansky,1 Isaías S. Paiva,2 Evelyn Kahn,3 Márcia G. Ribeiro4

Abstract

Objective: to share knowledge and information about the peculiarities of the Freeman-Sheldon syndrome, especially concerning the high risk of recurrence of its recessive type in siblings, and to stress the importance of genetic counseling for families after the birth of an affected child.

Description: the authors describe and comment two pediatric cases of the Freeman-Sheldon syndrome in siblings born to healthy parents. These two cases present significant peculiarities that contradict the findings of the medical literature, obtained through bibliographic research about the subject. The cases described here corroborate the existence of a recessive type of the Freeman-Sheldon syndrome. In spite of the fact that some authors suggest a high frequency of severe neurological impairment in this type of syndrome, the two cases we analyzed did not show any apparent manifestation of such sequelae.

Comments: the Freeman-Sheldon syndrome is heterogeneous not only in its clinical presentation but also in its genetic transmission. It is very important to be informed about the existence of more than one form of hereditary transmission of this syndrome, since genetic counseling should take into consideration all possibilities. In these cases, the use of empiric risks of recurrence would be justified.

Introduction

Craniocarpotarsal dysplasia was first described by Freeman and Sheldon in 1938,1 and it is a morphologically well-defined syndrome that results in a dysmorphic status combining bone anomalies and joint contractures with characteristic facies. In respect for the two authors, the disease is also known as Freeman-Sheldon syndrome (FSS). It is part of the nosologic group of pathologies currently known as distal arthrogryposis.2

At first, it was understood that the syndrome was very rare, but up until 1990 there were up to 65 cases reported in the literature.3 Both sexes are affected equally. The intelligence of patients is usually reported normal, though there is are occasional reports of association with mental retardation, especially in cases with combined important structural anomalies of the central nervous system.

The main bone anomalies in limbs of FSS patients are camptodactyly with ulnar deviation of the fingers and talipes equinovarus. The characteristic facies typically include prominent supraorbital ridge, sunken eyes, telacanthus, short nose and colobomata of the nostrils, long philtrum, high narrow palate, and marked microstomia and microglossia (small tongue). The facies are usually flattened and the physionomical expression rarely changes, as in a mask-like face. In general, there is an “H”-shaped cutaneous dimpling on the chin.

1. Professor, Department of Pediatrics, School of Medicine, UFRJ; chief of the Genetics Service (IPPMG), UFRJ; head of the Genetics Department, Brazilian Pediatric Society (SBP).
2. Trainee, Genetics Service (IPPMG), UFRJ.
3. Associate professor, Department of Pediatrics, School of Medicine, UFRJ; Genetics Service (IPPMG), UFRJ.
4. Assistant professor, Department of Pediatrics, School of Medicine, UFRJ; Genetics Service (IPPMG), UFRJ.
Most reported cases of FSS occur sporadically with no family history of the disease, though there are reports of a specific pattern of autosomal dominant inheritance in several families. Temtany and McKusick observed that FSS affected two generations of three different families. However, there are also reports of the syndrome suggesting a autosomal recessive inheritance; in other words, of affected children born to parents who were clinically normal but possible carriers (heterozygotic) of the gene responsible for the syndrome. It is possible to posit, then, that FSS may be heterogeneous from the genetic and/or clinical presentation point of view; in this sense, genetic counseling of parents of FSS children is truly challenging.

Our objective is to report the cases of two siblings affected by recessive autosomal FSS emphasizing the preventive relevance of genetic counseling, considering that these families will be at high risk for having more children with FSS.

**Case report**

**Case 1**

TAMC, a Caucasian girl, was referred to the Genetics Service of the Martagão Gesteira Puerculture and Pediatrics Institute (Instituto de Puerculture e Pediatria Martagão Gesteira - IPPMG) at the Universidade Federal do Rio de Janeiro at age 23 months. TAMC was born to a second unplanned and undesired gestation but with complete prenatal care and no intercurrences. The mother was 33 years old and in her third gestation and delivery. Fetal movements were reported following the third month of gestation. There was no history of maternal exposure to medication or radiation. Patient was a full term baby from instrumental delivery (forceps) due to prolonged expulsive phase of labor and with cephalic presentation. Normal hydramnios. The baby presented a low cry at birth. According to the mother, TAMC was cyanotic at birth, though she was not aware of the Apgar score. Birthweight of 2,910 g and length at birth of 47 cm. There were no perinatal intercurrences and baby was discharged from the hospital together with the mother.

Patient has a four-year old sister who is apparently normal and a five-month old brother (case 2) who has a similar phenotype. There is no history of previous diseases. Shortly after the birth of TAMC, the mother sought the services of a Genetic Clinic where, according to the mother, she was told her daughter had a syndrome that would not have great effect on her cognitive development; the mother reportedly was also told that the risk for the same problem occurring in another gestation was extremely low.

Until the present time, TAMC apparently presents normal motor development. The baby was able to hold her own head up at three months of age, to sit at six months of age, to crawl at nine, and to walk at 12. She spoke her first words at approximately 12 months of age and currently, at 23 months, her vocabulary includes several words. Cognitive development is apparently appropriate for chronological age. Vision and hearing, according to the mother, are apparently normal. Dentition started at six months of age.

Physical examination indicated weight = 9,100 g (below the 2.5 percentile); height = 79 cm (below the 2.5 percentile); head circumference = 46 cm (2.5 percentile); chest circumference = 45 cm; pulse at 82 bpm. Cardiac auscultation indicated that sounds were phonetically normal, without murmurs. The lungs were free of any problems. Patient did not present visceromegaly. Spinal column without pathological deviations. Asymmetry of the facies and head. Narrow and asymmetric forehead. Telacanthus. Short nose and colobomata of the nostrils. Long philtrum. Puckered lips (fused commissura labiorum) mimicking the act of whistling (Figure 1). “H”-shaped cutaneous dimpling on the chin. Micrognatia. Small tongue, high-arched palate, and poor teeth occlusion. Short neck. The hands were contracted and presented ulnar deviation of the fingers. Left hand with single palmar flexion crease. Deviation of the digitus quintus. Osteotendinous reflexes presented adequate response. Mild hypoplasia of the external genitalia. Apparently normal hearing. Patient was calm and interacted well with the examiner.

**Case 2**

CEFC is a five-month old infant who is active and smiles easily following stimulation by the examiner. He was born to a third and equally unplanned and undesired gestation but with complete prenatal care. The mother had urinary infection and anemia during gestation. Fetal movements were reported following the second month of gestation. Patient was a full term baby from C-section with adequate weight for gestational age and cephalic presentation. Normal hydramnios. Normal placenta and umbilical cord (sic). Born without perinatal asphyxia. Birthweight of 3,450 g and length at birth of 49 cm. There were no perinatal intercurrences and baby was discharged from the hospital together with the mother.

Patient had pathological history of urinary infection on the first month of life and anemia, which had already been controlled. CEFC apparently presents normal neuropsychomotor development for chronological age. Patient was able to hold his own head up after the third month of life. Physical examination indicated weight = 4,570 g (below the 2.5 percentile); height = 58 cm (2.5 percentile); head circumference = 44 cm (5.0 percentile); pulse at 88 bpm. Cardiac auscultation indicated that sounds were phonetically normal, without murmurs. The lungs were free of any problems. Palpable liver edge on right costal margin.
Figure 1 - Case 1: characteristic facies, showing telacanthus, short nose, colobomata of the nostrils, puckered lips (whistling face type), cutaneous dimpling on the chin, and micrognatia

Morphological examination indicated asymmetry of the facies and head. Relative macrocephalia. Narrow and asymmetric forehead. Telacanthus. Short nose and colobomata of the nostrils. Long philtrum. Puckered lips (fused commissura labiorum) mimicking the act of whistling (Figure 2). Cutaneous dimpling on the chin. Micrognatia. Small tongue, high-arched palate, and short neck. Camptodactyly with ulnar deviation of the limbs; adduction contracture of the thumb. Single palmar flexion crease on both hands. Talipes equinovarus with contracture of the toes (Figure 3). Good tonus. Osteotendinous reflexes presented adequate response. Nonpalpable left-side testis in the scrotum or in the inguinal or perineal regions, characterizing unilateral cryptorchidism.

Relatives

The mother presented normal facial expression (Figure 4). The father died at age 24 as a victim of a robbery but, according to the mother, did not have deformities of the face or limbs. A picture of the father examined at our services confirmed the information given by the mother. Parents were not consanguineous. Other more distant relatives such as grandparents, uncles, and aunts from either the father’s or the mother’s side were not examined; however, they were reported to us as apparently normal.

Discussion

FSS is understood as part of a group of disorders that concur with congenital multiple contractures. A cengenital contracture is defined as a structural deformity that hinders normal flexion and/or extension of a specific area of the body. The presence of contractures in one or more areas of the body of newborn infants is usually called arthrogryposis. This term is, however, merely descriptive and not pathognomonic nor diagnostic. Antley et al.12 established the diagnostic criteria for FSS. In an attempt to classify the distal arthrogryposis, Bamshad et al.13 identified a total nine disorders related to FSS; in the classification of the authors, FSS was named distal arthrogryposis type 2A.

Interestingly, it is common for FSS children to be considered as simple cases of arthrogryposis before final diagnosis of the syndrome. However, not all arthrogryposis children have FSS. Likewise, the presence of craniofacial deformities suggestive of FSS but not concomitant with arthrogryposis are a rare condition, and the deformities alone do not allow for diagnosis of FSS. Toydemir et al.14 described the only case in the literature until the present time related to a child with whistling face phenotype without limb abnormalities; the patient was born to normal and nonconsanguineous parents.

Craniofacial anomalies of FSS are specific and usually resemble the appearance of an individual who is whistling. Contribute to this characteristic facies the puckered lips and insufflated cheeks. Moreover, patients usually present combined microglossia and micrognatia; high-arched palate;

Figure 2 - Case 2: narrow and asymmetric forehead, telacanthus, short nose and colobomata of the nostrils, microstomia (whistling type), cutaneous dimpling on the chin, and flexion contracture of fingers.
prominent supraorbital ridge; sunken eyes; telacanthus; and occasional cases of strabism or palpebral ptosis.

Children with FSS usually present speech impediments, which are more marked in cases that concur with hypoacusis. In general, it is always important to investigate hearing impediments in cases of FSS, especially those with more marked speech disorders that could be aggravated by hypoacusis. Dysphagia is a frequent clinical manifestation reported by parents and could be one of the factors responsible for eating disorders, especially regurgitation and vomit. In addition, microstomia alone can make swallowing and chewing of certain foods together with the possibility of concomitant orthodontic anomalies. Failure to thrive, growth deficit, and respiratory complications that threaten the life of the patient are other relatively frequent intercurrences in pediatric FSS patients. Structural anomalies of the oropharynx and upper airways, which are commonly diagnosed in these patients, are a constant concern in cases of need for general anesthesia - not uncommon due to the various types of corrective surgery that are usually necessary in FSS. Among the several studies that approached this matter specifically, we would like to emphasize that of Munro et al.,15 which was directed to pediatric patients. Often times, tracheal intubation via direct laryngoscopy cannot be carried out in FSS pediatric patients. Robinson16 reported a case of FSS combined with severe upper airway obstruction that required neonatal tracheostomy.

Despite the fact that most cases of FSS are sporadic, it is accepted that there are two types of hereditary transfer of the syndrome. A more frequent type, autosomal dominant inheritance, and a more rare one, autosomal recessive inheritance. The understanding of genetic heterogeneity of this syndrome is very important for the process of genetic counselling of families. The greatest difficulty lies in cases following the birth of a first case of the syndrome in a family of apparently normal parents. These cases can be misinterpreted as a sporadic dominant mutation and the family be informed that the risk for recurrence in a next gestation would certainly be low. That is exactly what happened to the family in our case, who sought genetic counselling after the birth of TAMC with FSS. By considering that there are cases of FSS with autosomal recessive inheritance, for a risk of recurrence of 25%, it is imperative to present these families with the empirical risk for another case of FSS that would take into account all the
possibilities of transfer of the gene responsible for the syndrome. In the case of the family reported by Alves and Azevedo,17 the apparently normal parents of two FSS children were consanguineous, which is relevant for cases of autosomal recessive inheritance.

Our case report is important in the sense that it corroborates the occurrence of the recessive form of FSS, which had already been suggested by other authors. Bekir et al.18 are among those who described the case of two siblings affected by FSS and who were born to normal parents. Despite the syndrome being a result of autosomal recessive inheritance, the authors, nevertheless, indicated that this could be explained by genetic expression of the mutant gene in one of the parents.

Important neurological abnormalities in FSS children were recently described by Lev et al.18 The authors admitted the existence of various different forms associating whistling face syndrome with joint contractures; these forms varied from autosomal dominant without neurological involvement to autosomal recessive generally with different levels of neurological involvement. Sener19 described in detail the magnetic ressonance imaging findings in the brain of FSS patients. In our case, there is no evidence of neurological involvement of neurosensory hearing loss up until the present time, despite the pattern of autosomal recessive inheritance. Zampino et al.20 also described a sporadic case of FSS in a boy with acute hypertonicity, dysphagia, cerebellar atrophy and brainstem atrophy in addition to associated hearing loss. The authors suggested that primary brain anomalies can explain various manifestations of the syndrome; moreover, they also suggested that thorough investigation for CNS and auditory abnormalities should be part of the initial work-up of FSS patients.

During the past few years there have been attempts to map the gene responsible for the FSS. Following the proof that FSS has a heterogenous clinical presentation, which results in distinct subgroups of affected subjects, it is possible that one of these subgroups may follow from a mutation of a specific gene. Up until this date, only the genes of disorders correlated with FSS have been mapped. Bamshad et al.21 in 1994, mapped the pericentromeric region of chromosome 9, which is responsible for distal arthrogryposis type 1A, more specifically. In 1996, this same group of investigators22 was able to map the gene responsible for distal arthrogryposis type 2B to the chromosone 11. One of the difficulties for mapping the gene for FSS (distal arthrogryposis type 2A) is the very small number of families with several individuals who were affected by the disorder. Until the gene for FSS is mapped, it is impossible to carry out prenatal diagnosis of the disorder through direct DNA analysis. However, Robbins-Furman et al.23 were able to carry out prenatal diagnosis of FSS in a 20-week old fetus using positive family history and ultrasonographic findings. The authors were based on ultrasonographic features of abnormalities of the extremities of the fetus.

The follow-up of FSS pediatric patients requires support and special care including prolonged orthodontic and orthopedic treatment. Physical therapy can improve gait whereas speech and hearing follow-up can be used to assess speech impediments. Surgical correction of microstomia is important from both the aesthetic and functional points of view in relation to food intake; in this sense, others have reported good results.24

References

Correspondence:
Dr. Gerson Carakushansky
Rua General Artigas, 104 - apto. 401 - Leblon
CEP 22450-010 – Rio de Janeiro, RJ, Brazil
Phones: +55 21 294.0640 / +55 21 547.6838
Fax: +55 21 540.8834
E-mail: gercar@vento.com.br