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Freeman-Sheldon Syndrome Associated with Hemophilia-A in a Newborn

Bir Yenidoğanda Freeman-Sheldon Sendromunun Hemofili A ile Birlikteliği

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Abstract

The Freeman-Sheldon syndrome (FSS) (whistling face) is a congenital autosomal dominant disease (rarely described in its autosomal recessive form) characterized by small "whistling" mouth, a flat mask-like face, joint contractures (commonly involving the fingers and hands) and underdevelopment of the nasal cartilage. Other clinical features include full forehead, deep set eyes, epicanthal folds, high palate, H-shaped cutaneous dimpling on the chin, ulnar deviation of the hands, seizures, and dislocation of the hip. A 10-day-old male newborn was admitted to our neonatal intensive care unit with jaundice and hyperthermia. He had fever of 42.5°C, small whistling mouth, a flat mask-like face, joint contractures of the fingers, and ulnar deviation of the hands. The parents were consanguineous and one of the boys died when he was 1 years old due to intracranial hemorrhage. To our knowledge, there have been more than 60 cases diagnosed with FSS. This is the first reported case of Freeman-Sheldon syndrome associated with hemophilia A and the second case of FSS associated with fever without anesthesia.

Keywords: Whistling face syndrome, newborn, hyperthermia, hemophilia

Öz

Freeman-Sheldon sendromu, ısıklı çalar şeklinde küçük ağız, maske şeklinde yüz, eklem kontraktürleri (özellikle el ve parmaklarda), gelişmemiş burun kıvrımağı ile karakterize otozomal dominant (nadiren otozomal resesif olgular da bildirilmiştir) geçiş gösteren bir hastalıktır. Diğer klinik bulguları; geniş alın, derin yerleşimli gözler, epikantal kıvrımlar, yüksek damak, H şeklinde çukurlaşan çene, ellerin ulnar deviasyonu, nöbetler ve kalça çıkığıdır. Yenidoğan yoğun bakım ünitemize 10 günlük erkek hasta sarılık ve yüksek ateş nedeniyle yatırıldı. Hastamızın 42,5°C ateşi, ısıklı çalar şeklinde küçük ağız, maske şeklinde yüzü, parmaklarda eklem kontraktürleri, ellerinde ulnar deviasyonu vardı. Anne baba akraba idi ve 1 yaşında bir erkek çocuklarını intrakraniyal hemoraji nedeniyle kaybetmişlerdi. İngilizce literatür taramalarında 60 olgudan fazla Freeman-Sheldon sendromu olgusu bulunduğu görülmekle birlikte olgumuz hemofili A ile birlikteliği olan ilk, anestezi almadan hipertermi görülen ikinci olgudur.

Anahtar Sözcükler: Isıklı çalan yüz sendromu, yenidoğan, hipertermi, hemofili

Introduction

Freeman-Sheldon syndrome (FSS) is a congenital autosomal dominant disease (rarely described in its autosomal recessive form) characterized by small "whistling" mouth (whistling face), joint contractures, commonly involving the fingers and hands, and underdevelopment of the nasal cartilage which makes the face look flat and

mask-like. Other clinical features include full forehead, deep set eyes, epicanthal folds, high palate, H-shaped cutaneous dimpling on the chin, ulnar deviation of the hands, seizures, and dislocation of the hip (1). The features of this syndrome is secondary to increasing tone of muscles (1,2).

FSS was first described in 1938 (OMIM 277720); less than 100 cases have been reported in the literature since

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then (1,3). Here, we describe a patient diagnosed as having FSS with hemophilia A. To our knowledge, this is the first reported case in the literature.

Case

A 10-day-old male baby was transferred to our neonatal intensive care unit (NICU) with hyperbilirubinemia. The baby was born at home. The labor was uneventful. The parents took him to a local hospital for feeding problems. At admission, he had fever (42.5°C-axillary), icteric skin and ecchymotic areas on both forearms. He was the fifth child of consanguineous parents. His mother had 6 brothers, all of whom had hemophilia A. One of her male children died at 1 year of age because of an intracranial hemorrhage due to hemophilia A. He, like our case, had also had fever which was thought to be a central fever due to intracranial hemorrhage. It is possible that he also had FSS and hemophilia A. In addition, the baby's uncles had dimples on their chins which were the sign of FSS.

On examination, the baby's face seemed dysmorphic. He had whistling face including small puckered mouth, thin-pursed lips, long philtrum, prominent cheeks, and broad forehead. The upper limbs had camptodactyly with ulnar deviation of fingers and wrists with contracture of thumbs in adduction (Figure 1, 2). A sepsis work-up was done with the following results: white blood cell: 9600/mm³ hemoglobin: 13.2 mg/dL, platelet: 329.000/mm³, polymorphonuclear leukocyte: 54%, lymphocyte: 40%, monocyte: 6% and C-reactive protein: 0.4 mg/dL (negative). Blood, urine and cerebrospinal fluid cultures were negative.



Figure 1. Typical Whistling face of the patient

Because of the ecchymotic areas on his skin and the family history of hemophilia A, we looked at prothrombin time, activated partial thromboplastin time, international normalized ratio and factor 8 and the results were: 20.8 sec, >120 sec, 1.75, and 0.7%, respectively. Abdominal ultrasonography revealed mild hepatomegaly. His cranial magnetic resonance imaging (MRI) disclosed delayed myelination and hypoxic-ischemic encephalopathy. Cervical MRI showed bulging on C5-6 and C6-7. During the follow up, he had cyclic fever of up to 38.5°C every 2 or 3 days. He had persistent tonic seizures at admission treated with phenobarbital and phenytoin. The baby had sucking and swallowing disorders and was fed via orogastric tube. He was discharged from the NICU when he was 30 days old still on orogastric tube feeding. At the 4 months of age, he was admitted to the hospital with severe respiratory distress and died on the 7th days of hospitalisation.

Discussion

FSS is known as distal arthrogryposis type 2A. Most of the features are secondary to increased muscle tone. The known genetic etiologies of distal arthrogryposis syndromes involve abnormalities of the contractile apparatus of fast-twitch myofibers. The children with FSS are recognized by the characteristic facial appearance and the associated joint abnormalities. The syndrome has three characteristics: deformity of the face, camptodactyly with ulnar deviation of the fingers and/or wrists and bilateral clubfoot. As babies, they have feeding difficulties (e.g., poor suckling, vomiting and regurgitation), failure to thrive, and respiratory problems. Complicating their condition are recurrent respiratory infections (2). There may be early mortality related to aspiration. Difficulties with speech and oral hygiene can be a problem. Speech therapy is beneficial. Microcephaly and mental retardation have been reported in about one third of these children (3). Neuroimaging abnormalities include cerebral-cerebellar and brain stem atrophy, enlarged cisterna magna and interhemispheric fissure, ventricular dilatation, and cerebral venous thrombosis (4-6). Our patient had abnormal myelination and hypoxic ischemic encephalopathy.



Figure 2. Ulnar deviations of the fingers and the hematoma of the wrist

Parents are given genetic counseling. Prenatal diagnosis is possible by level 2 ultrasound scan. In the second trimester of pregnancy, facial and limb abnormalities can be detected (7-9). Vimercati et al. (7) have prepared a standard chart for fetal lip width to detect these abnormalities. Individuals with FSS should be counseled that recurrent risk for FSS is 50% (1). Most cases of FSS in the literature were reported as sporadic, but it can also be in a form of autosomal recessive or X-linked recessive patterns (2). In addition, mutations in the embryonic myosin heavy chain (MYH3) gene at 17p-13.1-pter have been showed (10).

The treatment of FSS includes surgical correction of skeletal deformities (surgical procedures are performed mostly on the limbs) and improving respiratory function. The risk of malignant hyperthermia and postoperative pulmonary complications are very high in these patients (11). The surgical procedures are done mostly on the limbs. Difficulty with intubation is a common complication, with hyperpyrexia reported in FSS patients after anesthesia. It has been suggested that hyperpyrexia is due to induction of the anesthetic agents because of myopathy (2). Our patient is the second case reported in the literature who had hyperthermia without anesthesia (12). His hyperpyrexia was characterized by a fever of 38.3°C to 42.5°C once in a day persisting for two weeks.

This is the first case of FSS associated with hemophilia A in the literature and the second case of FSS associated with fever without anesthesia. We report this case to raise awareness of the neonatologists and geneticists about this rare syndrome and associated disorders as a result of consanguineous marriages.

Ethics

Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Bilge Tanyeri Bayraktar, Süleyman Bayraktar. Design: Bilge Tanyeri Bayraktar, Süleyman Bayraktar. Data Collection or Processing: Bilge Tanyeri Bayraktar, Süleyman Bayraktar, Hüseyin Arslan, Fatma Betül Çakır. Analysis or Interpretation: Bilge Tanyeri Bayraktar, Süleyman Bayraktar, Hüseyin Arslan, Fatma Betül Çakır. Literature Search: Bilge Tanyeri Bayraktar, Süleyman Bayraktar. Writing: Bilge Tanyeri Bayraktar, Süleyman Bayraktar.

Conflict of Interest: No conflict of interest was declared by the authors.

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