



Case Report

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A Rare Case in the Newborn: Craniofrontonazal Syndrome



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Abstract

Craniofrontonasal syndrome (CFNS) is a very rare X-linked inherited disease characterized by abnormalities in the head and face, hands and feet, and certain skeletal bones, first described by Professor Michael Cohen from Canada in 1979. The phenotypic trait varies greatly among affected individuals; The syndrome is more common in girls and more severely affected than boys. The incidence of the disease is rare.

Keywords: Newborn; Craniofrontonasal syndrome; Craniosynostosis

Introduction

Craniofrontonasal syndrome (CFNS) (OMIM #304110) was first described by Cohen in 1979 and is an X-linked disease caused by mutations in the Ephrin B1 gene (EFNB1) located on the short arm of the X chromosome (Xp13.1) [1,2]. Affected girls present with the clinical picture, coronal craniosynostosis (CS), frontal prominence, hypertelorism, depressed nasal bridge, bipolar nose, craniofacial asymmetry, downward-sloping palpebral fissures, curly and curly hair, syndactyly, and longitudinal striation on the

nails. Interestingly, many symptomatic hemizygous men show only hypertelorism with no other congenital anomalies or major facial dysmorphism [3,4]. It is also possible that craniofrontonasal syndrome may be a gender-limited disorder, which is more severe in girls, explained by the differential interaction of the mutant gene with sex-specific developmental pathways [5]. We wanted to discuss the case, which was diagnosed as craniofrontonasal syndrome, in order to be seen as rare and to be educational, in the light of the literature.



Figure 1: Pathological facial appearance of the patient.

Case Report

A female baby born by cesarean section from a 28-year-old mother was admitted to the neonatal intensive care unit for diagnosis and treatment because of its syndromic appearance. The other two siblings of the patient, whose pregnancy follow-ups were not regular and there was no feature in her family history, were alive and healthy. In the first examination of the patient, body weight was measured as 2700g (25-50 p), height 47cm (25-50 p), head circumference (10-25 p). The patient had pathological physical examination findings of brachycephaly, frontal bossing, hypertelorism, slightly downward sloping palpebral fissures, wide nasal bridge, bifid nasal tip (Figure 1). The neck was short and low ears were present. Nipples were wide and asymmetrically located. The patient's entire abdomen and cranial ultrasonography and echocardiography were normal. Craniosynostosis was detected

in the patient's brain magnetic resonance imaging. Karyotype analysis was sent from the patient and it was normal as 46,XX. A mutation in the EFNB1 gene was found in the patient who was thought to have Craniofrontonasal syndrome based on clinical and radiological findings. The patient was discharged from the neonatal intensive care unit after 21 days postnatally with recommendations.

Discussion

The classic definition of CFNS includes facial asymmetry due to coronal craniosynostosis, hypertelorism, broad or bifid nasal tip, and brachycephaly. However, clinical manifestations are highly variable even within the same family. Except for craniofacial malformation, extracranial features are not uncommon [6]. The clinical findings of CFNS are summarized in Table 1 [7].

Table 1: Clinical features and frequencies of CFNS [7].

| Frequency | Head and Neck Anomalies | Neurological System | Skeletal and Genitourinary System | Dermatolojik Sistem |
|--------------|--|---|---|---|
| >%50 | Hypertelorism, frontal prominence, facial asymmetry, broad or bifid nasal tip, brachycephaly, coronal suture craniosynostosis, high palate | Normal development, Strabismus | | |
| %10-%50 | Short neck Webbed neck | Corpus callosum hypoplasia or agenesis | Sprengel anomaly, Scoliosis, Breast asymmetry, Unilateral breast hypoplasia, Abnormal thorax | Limb asymmetry, syndactyly-like finger anomalies, clinodactyly and polydactyly, grooved nails, coarse and rough hair, low anterior hairline |
| Occasionally | Cleft lip and/or palate, Cranium bifidum occiput | Sensorineural hearing loss, Cerebellar dysplasia, Developmental delay, Cerebellar dysplasia, Deafness | Asymmetry of pectoral muscle, Axillary pterygium, diaphragm hernia, Umbilical hernia, Bicornuate uterus, Uterus or kidney duplication | Wide hallux, Joint laxity |

The interesting “genetic paradox” associated with CFNS can be explained by the specific features of the EFNB1 gene. The EFNB1 gene was identified as the gene that causes CFNS in 2003 and is located on the X chromosome in the Xq13.1 region. The EFNB1 gene encodes the transmembrane protein ephrin-B1, a ligand for ELK. Its main function is to control cell sorting, migration and growth, which are crucial for tissue morphogenesis [8]. In hemizygous males, due to random binding, the ephrin-B1 deficit may be compensated for by other ephrin molecules, resulting in a less severe clinical phenotype. However, in heterozygous girls, cell-cell interactions are more complicated in the presence of random X inactivation. With X inactivation, a mosaic pattern of broad-type and mutant ephrin-B1 proteins is present. The mutant protein will interfere with the broad type, a phenomenon known as cellular interference, and explains the “genetic paradox” seen in CFNS. Different X inactivation patterns may also explain the variation in expression within the family [7,8].

CFNS is an X-linked syndrome because females are affected while male carriers are not affected at all or show very mild abnormalities [1,2]. Often, the condition is not diagnosed in boys unless they are a member of a family known to have the disease or father of a girl with the disease. An affected woman has a 50% chance of her daughter or son getting the disease. An affected male will have the disease transmitted to all of his daughters, but not to any of the males [2,3]. In the differential diagnosis, (MIM 145420) is similar to the findings in craniofrontonasal syndrome such as brachycephaly, telecanthus/hypertelorism and wide nasal tip. However, the absence of craniosynostosis and brittle linear nails are the main points that distinguish the disorder from craniofrontonasal syndrome [9].

Management of CFNS is similar to that of other craniosynostotic syndromes and requires a multidisciplinary team approach. However, CFNS is more challenging on surgical technique due to variable craniosynostosis, craniofacial

asymmetry and hypertelorism. Craniosynostotic correction has been recommended for 3 to 6 months to prevent increased intracranial pressure. Facial bipartition for facial asymmetry and hypertelorism should be performed at approximately 5-6 years of age after eruption of the maxillary central teeth to prevent severe disruption of the occlusal plane. Correction of nasal deformity should also be done during the facial bipartition period and should be revised in the adolescence period when the skeletal system matures [10]. Since strabismus and dissociated eye movements are more common in CFNS, regular ophthalmologic examination is recommended for early detection of visual impairment and timely intervention [11].

Conclusion and Recommendation

Genetic counseling and a multidisciplinary approach can be beneficial for affected individuals and their families. Each new case will serve as a guide to help clarify the phenotype of craniofrontonasal syndrome in the future.

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