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CASE REPORT

PRENATAL DIAGNOSIS OF CRANIOFRONTONASAL DYSPLASIA LINKED TO THE X CHROMOSOME: CASE REPORT

Daniel Quintana-Hernandez [1,a,b], Yanisbell Fajardo-Peña [1,c,d]

Filiation:
[1] Hospital Materno Infantil Manuel Piti Fajardo, Mayabeque, Cuba
[2] Hospital Ginecoobstétrico Ramón González Coro, Mayabeque, Cuba
[a] Doctor of Medical Sciences
[b] Clinical Genetics Specialist
[c] Specialist in Comprehensive General Medicine
[d] Master in Medical Genetics

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Correspondencia:
Daniel Quintana Hernández
Email:
daniel.quintana@infomed.sld.cu

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ABSTRACT

Introduction: Craniofrontonasal dysplasia (CFND) is a rare malformation disorder that primarily affects the eyes, nose and forehead. Of all of them, hypertelorism is the main and invariable component. It occurs sporadically in most cases. Only a few cases diagnosed before birth have been reported in the literature. **Objective:** To describe a prenatally diagnosed case of X-linked craniofrontonasal dysplasia. **Case report:** 21-year-old pregnant woman with initial evaluation of increased genetic risk of hereditary disease due to a personal and family history of CFND. At 24 weeks of pregnancy, an ultrasound was performed at the Provincial Center for Medical Genetics of Mayabeque - Cuba, a confirmation consultation that described facial anomalies in a female fetus with hypertelorism, a wide nasal bridge and a half-open mouth maintained throughout the study. No facial clefts or other associated defects were reported. Genetic counseling was offered. Based on the background information obtained, the assessment of the prepared family tree and the reported ultrasound findings, it was concluded that it could correspond to a fetus affected by CFND. The couple requested voluntary termination of the pregnancy. Fetal necropsy confirmed the diagnosis of CFND. **Conclusions:** To make the prenatal diagnosis of CFND, fetal ultrasound phenotyping, analysis of family history and anatomopathological findings are the key to personalized genetic counseling that allows the couple the reproductive option they consider most appropriate.

Key words: Craniofrontonasal dysplasia, Prenatal diagnosis, Genetic counseling (Source: MeSH NLM)

INTRODUCTION

Craniofrontonasal dysplasia (NFD) is a rare malformation disorder that primarily affects the eyes, nose and forehead. It is defined by the presence of two or more of the following dysmorphisms: true ocular hypertelorism, anterior occult bifid skull covered only by skin (cranium ocultum bifidum), widening of the nasal root, midfacial cleft affecting the nose, upper lip and palate, unilateral or bilateral cleft of the nasal wing, lack of formation of the nasal tip and V-shaped or widow's peak frontal hairline. Of all of them, hypertelorism is the main and invariable component. (1)

Occasionally, other features such as ocular changes, intellectual disability, ankyloglossia, cleft lip, nasal cutaneous appendages, hearing loss, and agenesis of the corpus callosum have been reported. (2)

The genetic aspects of craniofrontonasal dysplasia are not well defined. Recent studies link it to mutations in homeobox ALX genes, which function as transcription factors involved in the development and migration of neural crest cells. It can manifest in syndromic or isolated forms. It occurs sporadically in most cases; however, cases with autosomal dominant and X-linked inheritance patterns have been reported, as well as by 22q11 microdeletion.

It has been suggested that it is a type of developmental field defect, resulting from the arrest of the migration of the olfactory epithelium into the nasal capsule between the fourth and sixth week of embryofetal development. (1,3)

Only a few cases diagnosed before birth have been reported in the literature. (1) The aim of this article is to present a prenatally diagnosed case of X-linked craniofrontonasal dysplasia.

CASE PRESENTATION

A 21-year-old pregnant woman at 24 weeks of pregnancy, with an initial assessment of increased genetic risk of hereditary disease due to personal and family history (maternal mother and grandmother) of DCFN. In the family history there are no others affected (**Figure 1**).

An ultrasound scan performed in the health area revealed a defect in the facial massif, which was evaluated in the confirmatory consultation of the Provincial Center for Medical Genetics of Mayabeque, Cuba. Systematic 2D fetal ultrasound described facial abnormalities in female fetus with hypertelorism, internal interorbital diameters for 28 weeks (above the 97th percentile), wide nasal bridge, and mouth half-open maintained throughout the study. No facial clefts or other associated defects were reported (**Figure 2**).

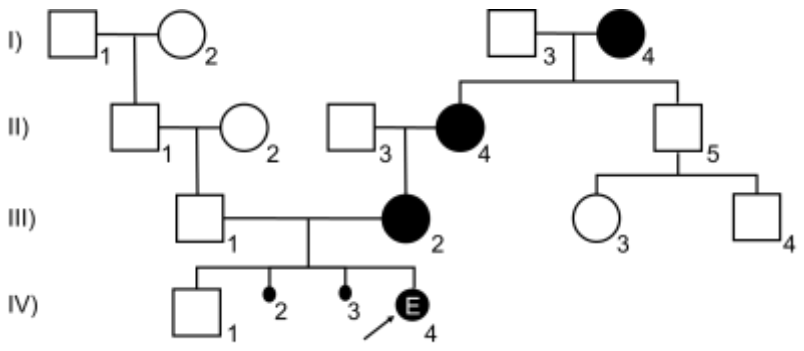
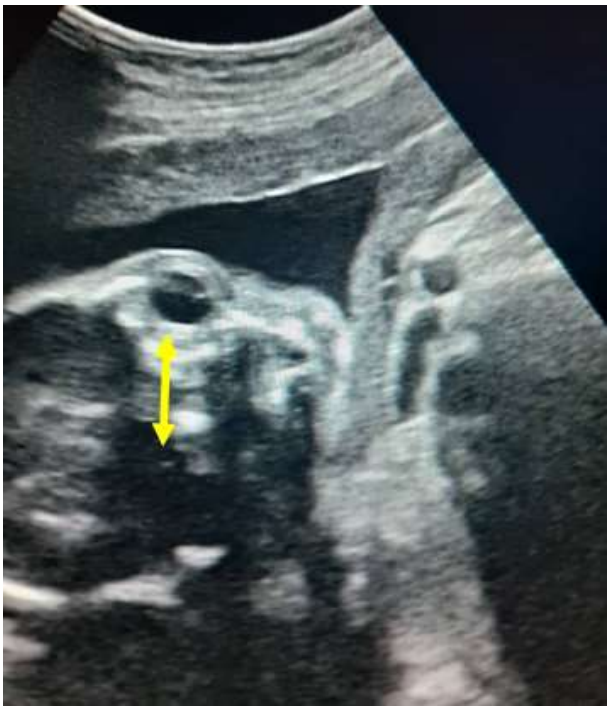


Figure 1. Family tree



Note hypertelorism (yellow arrow)

Figure 2. Ultrasound findings

Genetic counseling was offered. Based on the background obtained, the assessment of the family tree and the ultrasound findings reported, it was concluded that it could correspond to a fetus affected by DCFN. The couple requested a voluntary termination of the pregnancy. Interruption was induced with intravaginal prostaglandins, resulting in a female fetus with craniofacial malformations.

Fetal necropsy revealed hypertelorism, wide nasal bridge, absence of nasal tip, sublingual frenulum extending to the tip of the tongue (ankyloglossia), flattened nose, with nostrils widely spaced apart, short nasal columella, half-open mouth, syndactyly of the second – third finger of the left lower limb, thus confirming the pathological diagnosis of DCFN (**Figure 3**).

DISCUSSION

NFCD is a rare malformation with a variety of variable clinical phenotypes; however, it can occur alone or as part of a genetic syndrome. A thorough search for cranial and extremity malformations is recommended for differential diagnosis. In the case presented, the anatomopathological examination did not describe other extracranial malformations, so it was an isolated variant, which supports the scope of performing a detailed ultrasound of the entire fetal anatomy. (1,2)

Diagnosis is usually postnatal; However, a detailed ultrasound study of the fetus can identify a suggestive phenotype. The few reports found in the literature with prenatal diagnosis have been made in the second or third trimester of pregnancy. The earliest case detected was at 15 weeks, with a combination of craniofacial and limb defects corresponding to a syndromic variant (acromelic frontonasal dysostosis). (4)

Prenatal ultrasound reveals fetal defects that pose a diagnostic challenge for the sonographer and clinical geneticist. Polymalformative symptoms may not always be associated with known syndromes; Sometimes there are external features that cannot be seen due to the position and size of the fetus. (4)

Note hypertelorism, wide nasal bridge, absence of nasal tip, flattened nose, with widely spaced nostrils, short nasal columella, half-open mouth, syndactyly of the second – third finger of the left lower limb.

Figure 3. Fetus with craniofrontonasal dysplasia

Ultrasound evaluation of the fetus should be systematic, addressing each organ and organ system, to detect any concurrent structural abnormalities, as mentioned above. In addition to hypertelorism and nasal malformation, the suspicion of ankyloglossia was fundamental to the diagnosis due to the finding of keeping the mouth permanently ajar without protrusion of the tongue.

Some authors point out that MRI performed prenatally may be useful in establishing the diagnosis. (5)

In the authors' opinion, a detailed family history is an essential component of the comprehensive evaluation of these cases and can provide important information to reduce the differential diagnosis. In particular, attention should be focused on a family history of similar dysmorphic characteristics in the craniofrontofacial region, if possible to examine other affected limbs or, failing that, to evaluate medical reports or photographs that show the clinical manifestations described above. Finally, the preparation of a broad genealogy is essential to understand the possible patterns of inheritance of the disease.

An important component of phenotyping is fetal autopsy, as shown in the report. It can complement other diagnostic tests by confirming the presence of structural abnormalities and other features, as well as identifying additional defects that were not previously recognized on prenatal imaging. (6,7)

The treatment strategy for cases with craniofrontonasal dysplasia is not well established due to its low prevalence and clinical variability. However, craniofacial surgery is required in multiple stages, in which poor aesthetic results are generally obtained, with the consequent psychological trauma for patients and relatives, mainly with impacts on self-esteem, hence it is ethically accepted that voluntary termination of pregnancy is offered in genetic counseling. (8-10)

It is concluded that in order to make the prenatal diagnosis of DCFN and establish a possible pattern of inheritance, fetal ultrasound phenotyping, analysis of family history and anatomopathological findings are key; This guarantees a personalized genetic counseling process that allows the couple to decide on the reproductive option they consider most appropriate.

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Contributions:

Daniel Quintana Hernández: Performed the bibliographic review, translation of articles, analysis and discussion of the information, writing of the document, review, correction and approval of the manuscript. **Yanisbell Fajardo Peña:** Performed the analysis, discussion of the information, correction and approval of the manuscript.