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Review Article

Craniofrontonasal Syndrome: A Rare Genetic Pathology - A Case Study: Detailed Clinical and Genetic Study and Literature Review

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Abstract

Isolated craniofacial dysplasia in children is a complex congenital anomaly characterized by malformations of the skull and face. This pathology can be influenced by specific genetic mutations. Here is an overview of the main aspects, focusing on the responsible genetic mutations, diagnosis, and therapeutic management.

Keywords: *Craniofrontonasal Syndrome; Genetic Pathology; Skull and Face*

Introduction

Dysmorphic syndromes in infants represent a diagnostic challenge due to their complexity and the heterogeneity of their etiological causes. These morphological anomalies, which primarily affect the face and skull, require precise clinical and genetic evaluation to determine the underlying pathology.

Patient and Method

This clinical case focuses on an 8-month-old patient residing in Taourirt, admitted with facial dysmorphia. Genetic study diagnosed an EFNB1 gene mutation, responsible for craniofrontonasal syndrome, a rare but clinically significant pathology.

Medical and family background

Personal history

The patient is from a regularly monitored pregnancy with prenatal consultations following standard protocols. No notable events occurred during the pregnancy, which was carried to term without major complications. The delivery was vaginal, with a normal Apgar score, indicating no signs of neonatal distress.

The first signs of facial dysmorphia were observed at birth. Despite normal weight and height growth, these morphological anomalies drew the attention of healthcare professionals.

The patient's nutritional evolution was satisfactory, with the introduction of solid foods at 6 months, following recommendations.

Psychomotor development showed normal milestones (smiling, social interaction, fine and gross motor skills), indicating neurological development appropriate for her age.

Family history

The family history revealed an unremarkable genealogical tree. There is no consanguinity between the parents, a factor often explored in recessive genetic pathologies. Additionally, the other children in the family are healthy, with no signs of dysmorphia or developmental disorders, ruling out possible autosomal dominant transmission affecting multiple family members.

Detailed clinical examination

Upon admission, the patient underwent a thorough clinical examination, highlighting the following anomalies:

- **Marked facial dysmorphia (Figure 1):**
  - Short, prominent forehead: Typical of certain craniofacial syndromes where premature suture fusion leads to skull deformation.
  - Pronounced nasal saddle: A nasal deformity often associated with developmental anomalies of the cartilage and nasal bones.
  - Low-set, poorly positioned ears: A characteristic sign of craniofacial developmental disorders, frequently observed in syndromic conditions.
  - Hypertelorism: Excessive spacing of the orbits, contributing to the distinctive nature of the facial dysmorphia.

Figure 1

- **Absence of neurological and psychomotor anomalies:** Despite the dysmorphia, the neurological examination revealed no signs of motor or cognitive deficits. The patient exhibits psychomotor development appropriate for her age, with good posture control and normal social interaction.
- **Absence of auditory or visual disturbances:** Initial tests revealed no hearing or vision impairments, although more in-depth examinations are planned at later stages to confirm these observations.
- No stunted growth.

Paraclinical explorations

TORCH serology

TORCH infections (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes) are often implicated in congenital anomalies. In this specific case, the serology was negative for all these infections, ruling out a prenatal infectious cause for the observed anomalies.

Malformation assessment

A detailed malformation assessment was conducted, including the following examinations:

- **Craniofacial CT scan (Figure 2a-2d):** The CT scan revealed significant structural anomalies, confirming a complex craniofacial dysmorphia with Grade 2 Tessier orbital hypertelorism and upper maxillary hypoplasia.

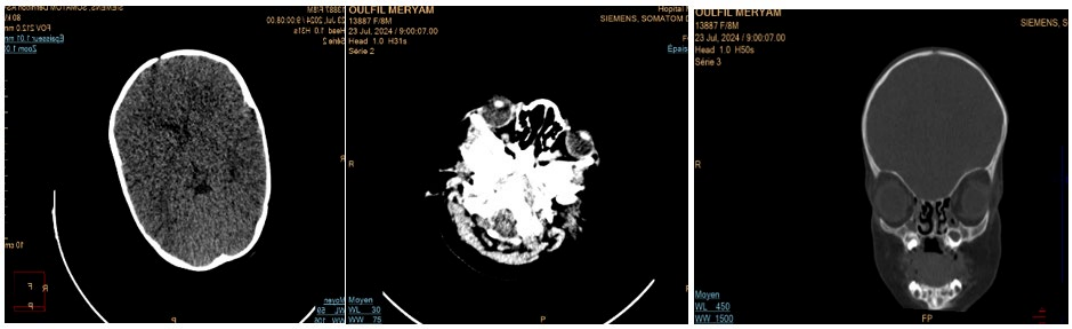

Figure 2a-2c

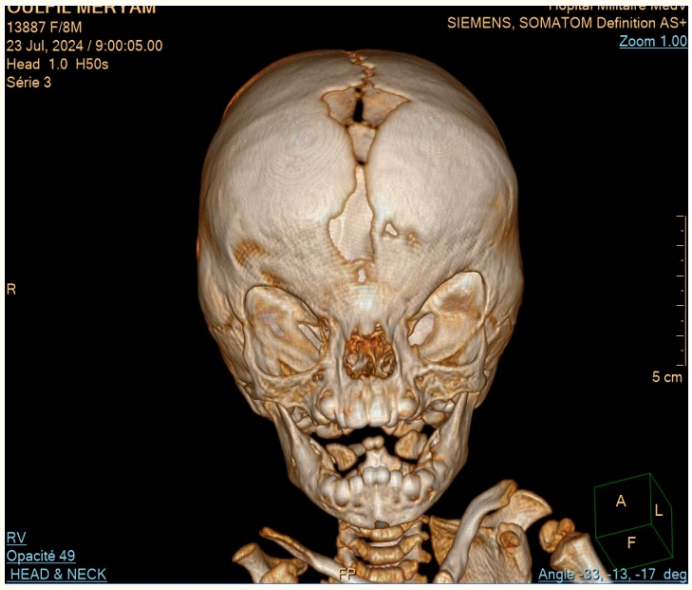

Figure 2d: *3D imaging showing craniofacial dysmorphia with cranial suture anomalies.*

- **Transthoracic echocardiography (TTE):** Given that many genetic syndromes involve cardiac anomalies, an echocardiography was performed. It showed no cardiac malformations, ruling out associated congenital heart disease.
- **Abdominal ultrasound:** This examination aimed to detect any internal organ anomalies, particularly renal or hepatic, which may accompany genetic syndromes. The results were normal.

After clinical and paraclinical examinations, craniofacial dysplasia syndrome was suspected, leading to the indication for genetic study.

Genetic diagnosis

The key step in this diagnostic process was performing a targeted genetic test. The patient's genome study revealed an EFNB1 gene mutation located on the X chromosome. This gene is responsible for producing ephrin-B1, a crucial protein in cell signaling, particularly involved in the development of craniofacial structures.

Implications of the EFNB1 mutation

Craniofrontonasal syndrome, linked to the EFNB1 gene mutation, is a rare genetic disorder with X-linked dominant inheritance. This syndrome primarily manifests as facial dysmorphia, hypertelorism, cranial bone anomalies, and sometimes skeletal malformations. The phenotypic variability observed in individuals with this mutation makes diagnosis complex, with some patients presenting more severe forms than others.

Therapeutic management and follow-up

The management of the patient requires a multidisciplinary approach:

- **Plastic and aesthetic surgery:** A consultation with a team of aesthetic surgeons was organized to plan corrective interventions. Initial steps will involve adjusting the shape of the forehead and nose to improve aesthetics and prevent potential functional issues related to breathing or vision.
- **Psychomotor follow-up:** Although psychomotor development is normal at this stage, regular follow-up is essential to monitor the acquisition of motor and cognitive skills over time, to detect any developmental anomalies that may appear.
- **Ophthalmological and ENT evaluation:** Regular consultations with vision and hearing specialists will be organized to ensure no sensory deficits related to craniofacial dysmorphia.

Discussion

History of isolated craniofacial dysplasia

Initial descriptions of craniofacial malformations date back to the late 19th century, with a progressive distinction between syndromic and non-syndromic forms. Early studies on craniosynostosis and other cranial anomalies laid the foundation for current research. The advent of genetic testing in the 20th century has better characterized these dysplasias [1].

Diagnosis of isolated craniofacial dysplasia

Diagnosis relies on clinical evaluation, medical imaging (cranial CT scan, MRI), and genetic tests.

Clinical presentation: Skull deformity in infants continues to be a diagnostic and therapeutic challenge. Deformational plagiocephaly is a common and relatively benign cause of skull deformation in infants that must be distinguished from more severe craniosynostosis, which occurs alone or as part of a syndrome. Examination of an infant's head from above can help the physician distinguish true lambdoid synostosis from deformational plagiocephaly. In infants with lambdoid synostosis, the posterior bulge is in the parietal region contralateral

to the flat part of the head. Deformational plagiocephaly causes an ipsilateral frontal bulge to the flat part of the head. In infants with lambdoid synostosis, the ear is displaced posteriorly toward the fused suture. In infants with deformational plagiocephaly, the ear is displaced anteriorly. Isolated sagittal synostosis is the most common type of craniosynostosis. Among the more than 150 craniosynostosis syndromes, Crouzon disease and Apert syndrome account for the majority of cases. The diagnosis of craniosynostosis relies on physical examination, simple radiography, and computed tomography. Progressive untreated craniosynostosis leads to inhibited brain growth and increased intracranial and intraorbital pressure. Infants should be evaluated as soon as they are diagnosed [2].

Medical imaging: The radiological classification of craniofacial dysmorphias is essential for precise diagnosis, surgical planning, and follow-up of patients with structural head and face anomalies. This classification is based on the detailed analysis of images obtained by various medical imaging techniques, such as radiography, computed tomography (CT scan), and magnetic resonance imaging (MRI). Here is a detailed classification of craniofacial dysmorphias:

1. **Craniosynostoses:** Craniosynostoses are characterized by the premature closure of one or more cranial sutures, leading to specific cranial deformations. They can be: a. Sagittal craniosynostosis (scaphocephaly). b. Coronal craniosynostosis (brachycephaly). c. Metopic craniosynostosis (trigonocephaly). d. Lambdoid craniosynostosis (plagiocephaly). e. Complex craniosynostotic: Multiple cranial deformations.
2. **Syndromes associated with craniofacial dysmorphia:** a. Crouzon syndrome: Upper maxillary hypoplasia. b. Apert syndrome: Marked midfacial hypoplasia. c. Pfeiffer syndrome. d. Treacher-Collins syndrome.
3. **Isolated facial dysmorphias:** a. Midfacial hypoplasia. b. Facial clefts. c. Macrognathia.

- **Isolated cranial malformations:** a. Microcephaly. b. Macrocrania. c. Platybasia. d. Basilar invagination [3].

Genetic testing: Sequencing genes involved in craniofacial development confirms the diagnosis and distinguishes isolated forms from syndromic forms.

Genetic mutations responsible for isolated craniofacial dysplasia

Genetic mutations are a key factor in the occurrence of these dysplasias.

- **ALX family genes (ALX1, ALX3, ALX4):**
  - ALX1 is associated with frontonasal dysplasia syndrome, characterized by severe facial anomalies.
  - ALX3 is also involved in frontonasal dysplasia, causing facial clefts and eye anomalies.
- ALX4 regulates cranial bone formation and is involved in non-syndromic forms of craniosynostosis [4].
- **EFNB1 (Ephrin-B1):**
  - EFNB1 mutations cause craniofrontonasal syndrome, characterized by asymmetrical cranial and facial malformations, often X-linked.
- **ZSWIM6 (Zinc finger SWIM-type containing 6):**
  - ZSWIM6 is linked to craniofacial and brain development. Its mutations are associated with syndromic facial dysplasia with polymicrogyria.

- **STECC1L (Staphylococcal enterotoxin receptor-like 1):**
    - This gene is involved in the development of facial structures derived from neural crests. Although less studied, its mutations could be linked to craniofacial anomalies [5].

Therapeutic management

a. Initial evaluation and surgical planning:

- Early diagnosis allows for planning surgical interventions before the deformation becomes too severe. Multidisciplinary teams, including neurosurgeons, craniofacial surgeons, and orthodontists, are essential for successful management.

b. Corrective craniofacial surgery:

- **Craniectomy:** Skull reshaping is performed by craniectomy to release fused sutures and correct malformations.
- **Distraction osteogenesis:** A technique used to lengthen and reshape cranial bones over several months in complex deformations [6].

c. Postoperative follow-up and complication management:

- Long-term follow-up includes regular radiographic examinations and managing functional disorders such as vision and speech problems.

d. Complementary care and psychological support:

- Orthodontic care and psychological support are necessary to improve the child's quality of life and prevent social complications related to physical appearance.

Therapeutic advances and emerging research

Gene therapies and 3D printing of bone grafts are emerging technologies that could transform the management of craniofacial dysplasias:

a. Gene therapies: Gene therapies are being developed to correct genetic mutations underlying craniofacial dysplasias.

b. 3D printing and bone grafts: 3D printing allows precise surgical planning and could be used to bio-print bone grafts tailored to each patient.

Conclusion

This case illustrates the importance of a multidisciplinary and rigorous diagnostic approach in dysmorphic syndromes. Through genetic study, the diagnosis of craniofrontonasal syndrome linked to the EFNB1 gene mutation was made, allowing for appropriate surgical management. This follow-up, combined with an early therapeutic approach, will enable the patient to improve her long-term functional and aesthetic prognosis.

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