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Prenatal diagnosis of 7p22.1 microdeletion including the ACTB gene: Baraitser-Winter cerebrofrontofacial syndrome

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Abstract

Microdeletions in chromosomal region 7p22.1, which include the ACTB gene and may lead to the onset of Baraitser Winter Cerebrofrontofacial Syndrome (BCFF), have a very low incidence, and its prenatal diagnosis is even more uncommon. Ultrasound findings, according to reported cases, may include abnormalities in the brain, face, abdomen, heart, and limbs. Given the limited documentation of this syndrome at the prenatal level, we present a case of prenatal diagnosis to strengthen the potential fetal phenotypic spectrum through ultrasound.

Keywords: Prenatal genetic diagnosis; 7P22.1 microdeletion; ACTB gene; Baraitser winter cerebrofrontofacial syndrome.

Introduction

Microdeletions involving the chromosomal region 7p22.1 are extremely rare. A critical region of 0.37 Mb has been proposed within this locus, encompassing the genes FBLX18, ACTB, FSCN1, RNF216, and ZNF815. However, most authors consider the haploinsufficiency of the ACTB gene to be responsible for the clinical manifestations associated with microdeletions in this region [1]. The Baraitser-Winter Cerebrofrontofacial Syndrome (BWCFF) is an infrequent disorder characterized by multiple congenital anomalies, caused by a pathogenic variant in either the ACTB gene (7p22) or the ACTG1 gene (17q25), both of which act through an abnormal gain-of-function mechanism. These genes encode cytoskeletal proteins, namely β-actin and γ-actin [2]. To date, as far as we are aware, only six cases with prenatal diagnosis have been reported globally [3-8]. The aim of this article is to expand the phenotypic spectrum of the syndrome, presenting a case report of a prenatal diagnosis involving a deletion of the 7p22.1 region that includes the ACTB gene.

Case report

This is a 37-year-old female patient, who was admitted for a detailed fetal anatomical ultrasound at 22.3 weeks of gestation. The patient denies any significant personal or family medical history. Regarding her obstetric history, she has experienced a spontaneous early miscarriage and two previous term pregnancies, both uncomplicated and resulting in vaginal deliveries with appropriate birth weights for gestational age. Both children are currently growing healthy. Her current pregnancy was conceived spontaneously with a new partner. As for other paraclinical follow-ups during her pregnancy, infection and HIV profiles were negative, and routine prenatal laboratory tests showed no abnormalities. The patient underwent a genetic screening ultrasound, which indicated a low risk for chromosomal abnormalities, with a nuchal translucency of 2.4 mm, the presence of a nasal bone, and no other relevant findings. In the anatomical ultrasound, the fetus was found to be growing at the 22nd percentile, with a head circumference at the 4th percentile (Z score

-1.8). Additionally, bilateral cleft lip and palate were observed, along with the presence of a central prolabium, a flat facial profile, and a broad nasal base (Figure 1). Due to the findings on this ultrasound, an invasive genetic study was recommended, including amniocentesis for G-banding karyotyping, FISH, and Comparative Genomic Hybridization (CGH) microarrays with SNP analysis, which was performed at 25.4 weeks of gestation. The report from the Comparative Genomic Hybridization (CGH) microarray with SNP analysis revealed a 342 kb microdeletion affecting the chromosomal region 7p22.1, classified as likely pathogenic. This deletion involves 10 HGNC genes and 5 OMIM reference genes, including the ACTB gene: Arr [GRCh38] 7p22.1 (5340111_5682145) x1. A critical region of 0.37 Mb was identified, encompassing the genes FBLX18, ACTB, FSCN1, RNF216, and ZNF815P. In a follow-up obstetric ultrasound, in addition to the facial defect, microcephaly was noted with a head circumference below the percentile 2. The patient was evaluated in a maternal-fetal medicine consultation, and the results of the genetic study were explained to the parents at 34.4 weeks of gestation. The potential prognoses for the fetus were discussed, and the patient was referred to genetic counseling. At 34.5 weeks of gestation, the patient presented to a tertiary-level hospital requesting a voluntary pregnancy termination under the current legal framework in the country. She was admitted to initiate the termination protocol and was assessed by a multidisciplinary team, including counseling for the patient and her partner. The patient underwent a fetal asystole protocol at 36 weeks followed by induction of labor. A male fetus was delivered, with an APGAR score of 0 at both the first and fifth minutes. In addition to the bilateral cleft lip and palate, a flat facial profile, low-set ears with folded helix, apparent hypertelorism with long eyelashes, and a bulbous, broad-based nose were noted (Figure 2). Both the placenta and the fetus were sent for pathological examination, which revealed no other relevant findings.

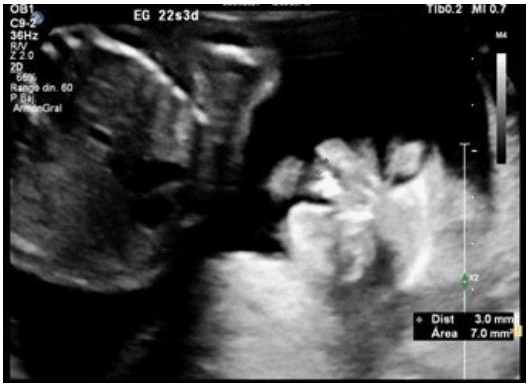

Figure 1: Clinical image

Discussion

There are few reports of microdeletions involving the 7p22.1 region, and since this region affects several genes, it is challenging to establish a clear genotype-phenotype correlation. However, pathogenic variants affecting the ACTB gene and ACTB haploinsufficiency, which are implicated in Baraitser-Winter Cerebrofrontofacial Syndrome (BWCFF), may be responsible for the clinical features observed in patients with this microdeletion [9]. Given the limited prenatal reports of 7p22.1 microdeletion involving the ACTB gene, fetal ultrasound findings

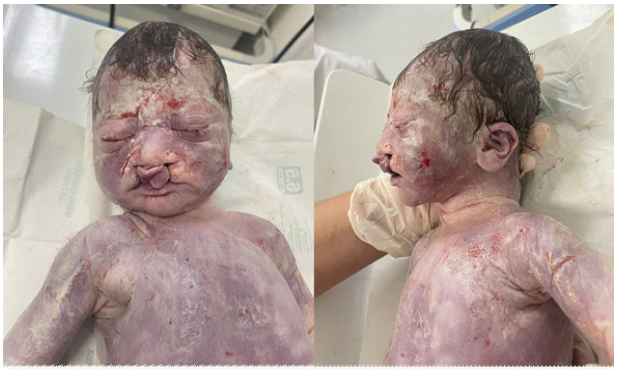

Figure 2: Clinical image

have been scarcely described. The purpose of this case report is to document and expand the phenotypic spectrum observable in utero. BWCFF was first described by Baraitser and Winter in 1988, following the presentation of three patients with coloboma, ptosis, hypertelorism, telecanthus, intellectual disability, and short stature. Since then, additional cases have been reported, including prenatal findings in the first trimester, such as increased nuchal translucency [6]. In follow-up ultrasounds, including anatomical ultrasounds, cerebrofacial abnormalities are the most characteristic, with mild ventriculomegaly, retrognathia, hypertelorism, flat facial profile, and cleft lip and/or palate being commonly observed [10,11]. Abdominal findings such as omphalocele, absence of the gastric bubble, hydronephrosis, and cystic kidneys have been documented [4-6]; cardiac findings, such as pulmonary stenosis, have recently been reported [5]; polyhydramnios [12] and clubfoot have also been described [3-13]. Postnatal additional findings in the cranial region include microcephaly, agenesis or hypoplasia of the corpus callosum, pachygyria, cerebellar hypoplasia, and ventriculomegaly [14]. In the facial region, findings such as coloboma, hypertelorism, highly arched eyebrows, long eyelashes, broad nasal base, and thin lips are commonly noted. Cardiovascular involvement may include ventricular septal defects, tricuspid regurgitation, bicuspid aortic valve, aortic and pulmonary stenosis [13]. Neurodevelopmental impairment manifests with cognitive delay, sensorineural hearing loss, epilepsy, and pachygyria. Other reported findings include short stature, delayed growth velocity, pectus excavatum, inguinal hernia, ectopic or duplicated kidneys, and cryptorchidism [1-13]. In our case, the postnatal abnormal findings were primarily craniofacial, including bilateral cleft lip and palate, flat facial profile, and broad nasal base, along with postnatal findings of low-set ears with folded helix and apparent hypertelorism with long eyelashes. In this article, we present the case of a prenatal diagnosis of a microdeletion in the 7p22.1 genetic region, which includes the ACTB gene and is responsible for Baraitser-Winter cerebrofrontofacial syndrome. We describe the fetus phenotypically through ultrasound and subsequently correlate the postnatal findings. This is a highly challenging prenatal diagnosis, which in our case, was made through Comparative Genomic Hybridization (CGH) microarray with SNP analysis, however, most of the other documented cases were diagnosed through exome sequencing. Following the results of the genetic study, genetic counseling becomes crucial regarding prognosis, management, the possibility of voluntary pregnancy termination depending on the country's legislation, and ultimately, considerations for a future pregnancy.

Conclusion

The prenatal diagnosis of the 7p22.1 genetic microdeletion and the mutation in the ACTB gene is highly challenging, with very few cases reported to date. It presents with a broad phenotypic spectrum, both prenatally and postnatally, which we aimed to further define with our report. However, the presence of the described ultrasound findings detected prenatally should prompt the recommendation for an invasive genetic study as early as possible. This will provide parents with the most comprehensive information regarding prognosis, management, and options for pregnancy termination in accordance with the legislation of their country.

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