CLINICAL REPORT

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Mandibulofacial Syndrome With Growth and Mental Retardation, Microcephaly, Ear Anomalies With Skin Tags, and Cleft Palate in a Mother and Her Son: Autosomal Dominant or X-Linked Syndrome?

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We report on a Brazilian mother and her son affected with mandibulofacial dysostosis, growth and mental retardation, microcephaly, first branchial arch anomalies, and cleft palate. To date only three males and one female, all sporadic cases, with a similar condition have been reported. This article describes the first familial case with this rare condition indicating autosomal dominant or X-linked inheritance.

Key words: mandibulofacial dysostosis; branchial arch; speech delay

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INTRODUCTION

Mandibulofacial dysostosis (MFD) is a heterogeneous group of disorders with abnormal craniofacial development that is or not associated with limb anomalies [Gorlin et al., 2001]. Among the conditions without limb involvement, the most common type is the Treacher Collins syndrome (TCS) [OMIM 154500]. About 80% of the patients with this condition are heterozygous for mutations in the *TCOF1* gene [Splendore et al., 2002, 2005; Teber et al., 2004; Dixon et al., 2007]. Other rare conditions with MFD as part of the phenotype have been reported, including MFD Toriello type [OMIM 301950], MFD Bauru type [OMIM 604830], MFD with macroblepharon and macrostomia [OMIM 602562], MFD with ptosis [OMIM 608257], and MFD with severe lower lid coloboma and cleft palate [Stevenson et al., 2007]. Till now, the pathogenesis of these conditions is unknown. Here, we describe a boy with MFD, growth and mental retardation, severe language delay, microcephaly, unusual ears with skin tags, and cleft palate. His mother also had the same craniofacial phenotype but without cleft palate, mental retardation, or language impairment. The phenotype observed in our case is very similar to that described by Guion-Almeida et al. [2006] in four Brazilian patients, suggesting that they present the same condition. Clinical and genetic aspects and differential diagnosis were discussed.

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The propositus (Fig. 1A,B), born in 2002, is the only child of nonconsanguineous parents. Pregnancy was unremarkable and he was delivered at term; birth weight was 3,370 g (50th centile) and length 48 cm (3rd–10th centile). Abnormal ears, cleft palate, and respiratory difficulties were noted at birth. His father was phenotypically normal but his mother presented a similar phenotype to that of her son. Evaluation of mother at age 25 years showed microcephaly, S-shaped palpebral fissures, epibulbar dermoid on the left side, zygomatic arch hypoplasia, thick lips, limited mouth opening, micrognathia, mildly asymmetric mandibular rami, and bilateral preauricular skin tags (Fig. 2A–C). The ears were small with a striking malformation of helices and antihelices and meatal

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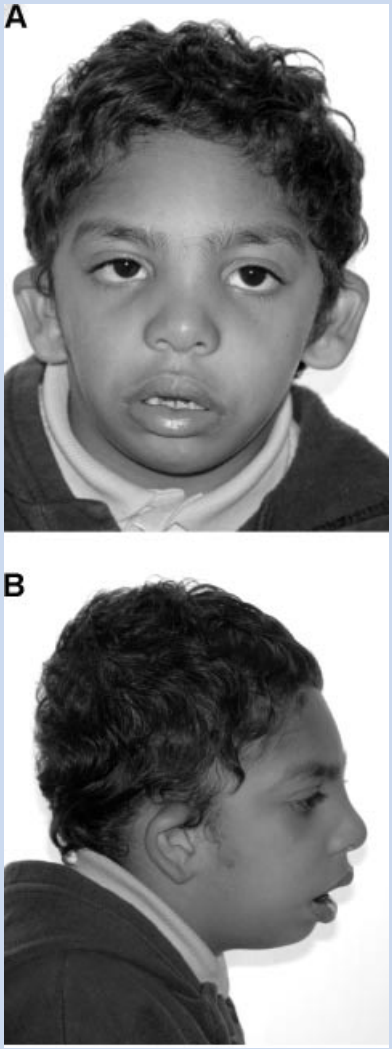

FIG. 1. A: Frontal view of the propositus. B: Lateral view of the propositus.

atresia. In infancy, the mother had mild motor development delay and learning difficulties.

Clinical examination of the propositus at age of $5^1/_2$ years showed weight of 20 kg (25–50th centile), height of 107 cm (10–25th centile), and OFC of 46 cm (<3rd centile). He had microcephaly, sloping forehead, frontal hirsutism, synophris, broad nasal root, S-shaped palpebral fissures, zygomatic arch hypoplasia, open mouth with thick lips, micrognathia, asymmetric mandibular rami, and cleft palate. The ears were small and cup-shaped with atretic meatus, preauricular skin tags, and pit on the right side. Motor development was normal; he sat without support at the age of 7 months and started to walk at the age of 13 months. Toilet skills were achieved at 4 years. At age $5^1/_2$ years, he had a significant delay in cognitive and language development. He understood very simple verbal orders; had no vocalizations, and used gesture communication. He was emotionally immature and related inadequately to persons. Radiographs of cervical spine were normal. Brain CT scan showed prominent posterior horns of lateral ventricles. Audiological evaluation showed bilateral moderate conductive hearing loss. Chromosomal analysis (450 bands) was normal. No pathogenic mutation in the *TCOF1* gene was detected in the propositus.

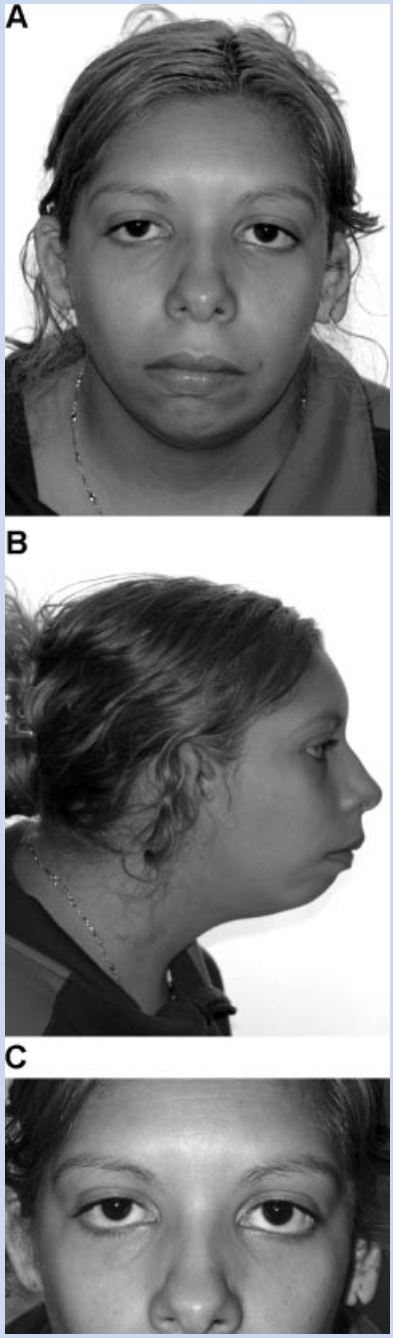

FIG. 2. A: Frontal view of the propositus' mother. B: Lateral view of the propositus' mother. C: Close-up of the mother's eyes showing epibulbar dermoid at the left side.

DISCUSSION

The patient and his mother display a typical facial phenotype fitting into the MFD group. The pattern of malformation including mi-

crocephaly, zygoma hypoplasia, unusual ears with skin tags, cleft palate, mental retardation, and language and speech delay was similar of that described by Guion-Almeida et al. [2006] in four isolated Brazilian cases. Severe feeding difficulties present in these previously reported patients were not observed in our propositus and, the language impairment, marked finding in this condition, was absent in the mother of our propositus. The mother also had an epibulbar dermoid. The striking facial appearance and craniofacial involvement in the mother and her son and the severe language impairment in the propositus, as in the other Brazilian published cases, strongly suggest that all patients have the same genetic condition. These families are unrelated and widespread throughout the country that become remote the possibility of a common haplotype.

In relation to differential diagnoses, the pattern of anomalies of our patients differs significantly from the well-established syndromes of MFD with or without limb involvements, such as TCS [OMIM 154500], Nager syndrome [OMIM 154400], MFD Toriello type [OMIM 301950], MFD Bauru type [OMIM 604830], Genée–Wiedemann syndrome [OMIM 263750], among others rare conditions. The epibulbar dermoid in the mother of the propositus suggested presence of Goldenhar anomaly [OMIM 164210], which could be excluded on a clinical basis.

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