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Mandibulofacial Dysostosis Guion-Almeida Type: A Syndrome to Recognize in Prenatal

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1. Abstract

Mandibulofacial dysostosis with microcephaly, Guion-Almeida type (MFDGA) is a rare multiple congenital anomalies syndrome characterized by malar and mandibular hypoplasia, microcephaly, ear malformations with associated conductive hearing loss, esophageal atresia, cleft palate and distinctive facial dysmorphism. Almost all affected individuals have developmental delay and intellectual disability. To date, more than 100 cases have been described in the literature. MFDGA is caused by heterozygous variants in the EFTUD2 gene. Considering the risk of a poor neurodevelopmental prognosis and the possibility of prenatal genetic diagnosis, MFDGA should be prenatally evocated.

Given the few reports of MFDGA prenatal findings, we report in this study, prenatal and autopsy findings of a fetus with MFDGA prenatally suspected and genetically confirmed after termination of pregnancy. We also analyze findings of the only six fetuses reported in the literature, to better characterize the prenatal clinical spectrum attributed to MFDGA. The seven pregnancies were characterized by ultrasound anomalies. Five pregnancies presenting a serious cerebral malformation, isolated or associated to other ultrasound anomalies, were terminated. The autopsy, performed on three of these five fetuses, had allowed a finer clinical diagnosis. A EFTUD2 mutation was found by molecular screening in all cases. To the best of our knowledge, no MFDGA prenatal criteria have been established, but several of postnatal signs could be antenatally seen if specifically and carefully searched. We propose to identify ultrasound prenatal signs that should lead to MFDGA diagnosis.

2. Case Report

A 26-year-old woman, gravida 2, P0 (1 abortion) was referred to the multidisciplinary prenatal diagnosis center of Nice University Hospital, at 22 weeks of amenorrhea (WA), for ultrasound (US) abnormalities.

The couple was healthy and nonconsanguineous. The family history was unremarkable for birth defects. There was no history of maternal diabetes or exposure to teratogens. Nuchal translucency measurement was evaluated at 1.8MoM. First trimester screening evaluated a low risk for Down syndrome.

At 22 WA, ultrasound assessment showed a single fetus with 15th-18th centile cephalic, abdominal, and femoral biometries. Estimated fetal weight was at 4th centile for the gestational age. Repeat Morphological ultrasound at 25 and 29 WA showed craniofacial abnormalities (Figure 1-2) associating bilateral, protruding, and asymmetrical dysplastic ears, low implanted with microtia and a left preauricular tag. The fetus presented also a posterior cleft palate (Figure 3) and a retrognathia. Transcerebellar diameter was

evaluated at 5th centile. Amniotic fluid index (AFI) was measured at 17cm (norm 8-18cm). Dopplers and fetal movements were normal.

Amniocentesis was performed at 24+4 WA and revealed a normal male chromosomal microarray (SNP-array Affymetrix, 750K). The US examination at 29 WA showed, in addition to abnormalities diagnosed at 22 WA, a moderate hydramnios with AFI at 25.2 cm and a 3rd centile transcerebellar diameter. A fetal magnetic resonance imaging was also performed and showed global brain biometry <10th centile with 2 weeks delayed gyration (Figure 4). Semicircular canals were normal and choanae were seen permeable. This syndromic association evoked us mandibulofacial dysostosis, MFDGA or other pathology with high risk of intellectual disability. The couple decided to terminate the pregnancy at 30 WA.

At the fetal autopsy, the weight was 1528g (25-50th centile), crown-heel length was 40 cm (50th centile) and head circumference was 27 cm (40th centile). Despite of the severe maceration, the fetus showed evident dysmorphic features (Figure 3) including bitemporal retraction with downward-slanting eyes. He had low-set, dysplastic round ears with microtia and lobule hypoplasia. The Crus helix of the right ear was connected to antihelix (crux cymbae sign) (Figure 2). He had retrognathia and posterior cleft palate (Figure 3). On the hands, we observed proximally placed right thumb. The internal examination did not reveal abnormalities especially for the digestive tract and the heart. The brain was unexaminable due to maceration and lysis.

Post-mortem X-ray was performed and was normal. A three gene-panel (HOXA1, EFTUD2 and CHD7) sequencing was performed on fetal DNA and identified a de novo heterozygous splice site variant c.2046-1G>T of the EFTUD2 gene (NM_004247.4). This mutation predicted to abolish the acceptor splice site of intron 20 and hence predicted to be pathogenic, confirming clinical diagnosis of MFDGA.

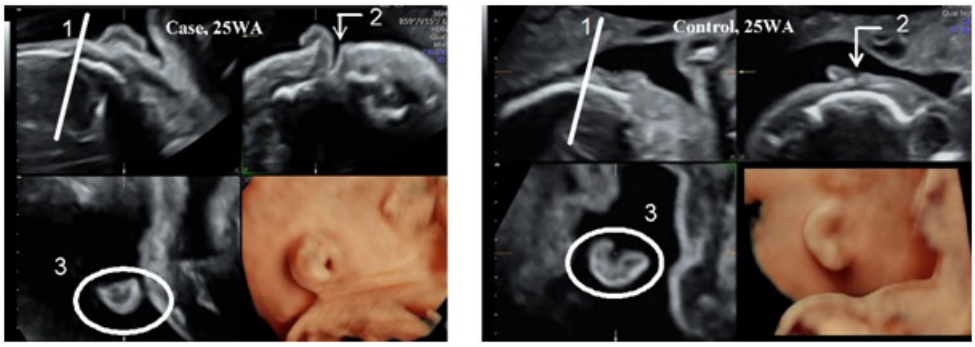

Figure 1: 25 WA 2D and 3D US:

1. Low-implanted ear: in coronal plane: the upper limit of the ear is lower than the temporo-parietal suture.
2. Wide external ear canal.
3. Dysplastic round right ear with microtia.

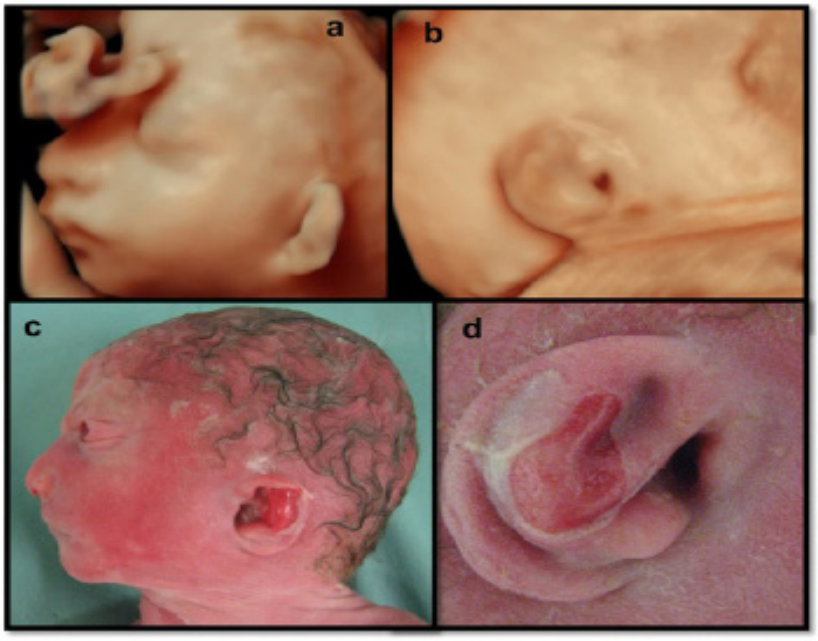

Figure 2: 29 WA 3D US and fetal autopsy

a,c: dysplastic left ear, low implanted, with microtia, high nasal root and retrognathia

b,d: dysplastic round right ear with microtia and hypoplastic lobule. The Crus helix of the right ear is connected to antihelix (crux cymbae sign)

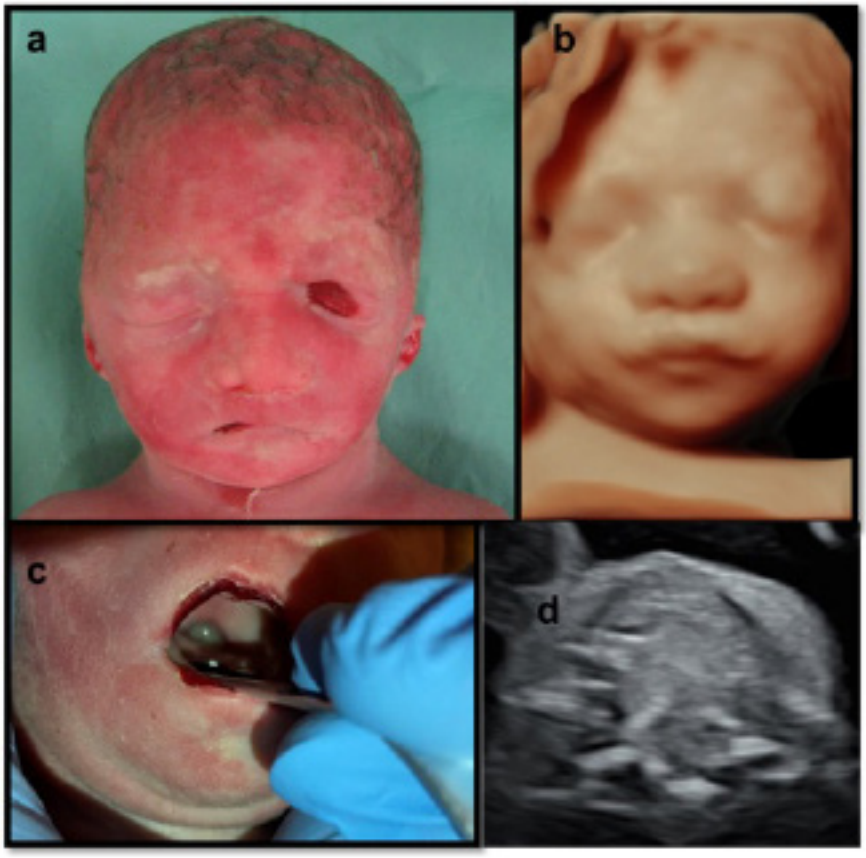

Figure 3: 29 WA US and fetal autopsy
a, b: dysmorphic facial features: bitemporal retraction with downward-slanting eyes and wide nasal base
c, d: Posterior cleft palate

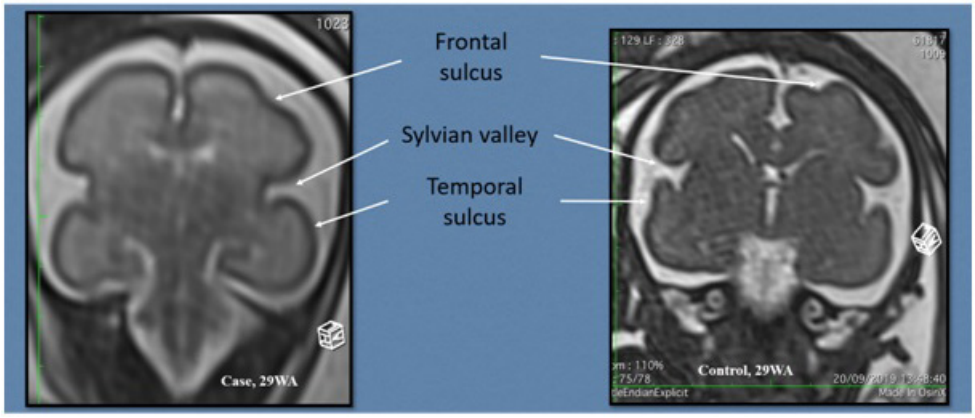

Figure 4: A fetal magnetic resonance imaging showing 2 weeks delayed gyration.

Table 1. Postnatal major criteria of MFDGA (Williams's et al [10]. Lines et al [4].)
MFDGA should be suspected in individuals with 3 or more of these features.

1. Mandibulofacial dysostosis Commonly characterized by malar and maxillary hypoplasia. Associated anomalies can also include midline cleft palate, choanal atresia, ear anomalies (see below).
2. Microcephaly Intellectual disability present in virtually all individuals with varied severity.
3. Characteristic malformations of the middle/outer ear. External ears are abnormal in virtually all individuals. Middle ears are abnormal in some individuals. Hearing loss affects about 75% of individuals (80% is conductive).
4. Esophageal atresia/Tracheoesophageal fistula
5. Characteristic dysmorphic features (including micrognathia, a relatively high nasal root with prominent ridge, everted lower lip, and (frequently) facial asymmetry).

Table 2: Ultrasound and autopsy findings of MFDGA

		Gordon et al.[5], Daphné et al.[8]			Mouthon et al.[14]		Xu B et al.[15]	Our case
		Fetus 1	Fetus 2	Fetus 3	Fetus 4	Fetus 5	Fetus 6	Fetus 7
USE	SGA/IUGR	low birth weight – 1 SD	ND	ND	-	-	-	SGA
	Microcephaly	-	ND	+	-	-	-	-
	Ear anomalies	-	ND	ND	-	-	-	Bilateral protruding, dysplastic low-implanted ears, microtia<-2SD
	Mandibular hypoplasia	-	ND	ND	+	+	+	+
	Malar hypoplasia	-	ND	ND	-	-	-	-
	cleft palate	-	ND	ND	+	+	-	+ posterior
	Preauricular tag	-	ND	ND	-	-	-	+ unilateral
	CNS malformation	Delayed gyration	Exencephaly	Cerebellar hypoplasia and delayed gyration	Cerebellar hypoplasia	Normal	-	Cerebellar hypoplasia and 2 weeks delayed gyration
	Hydramnios	-	ND	ND	-	-	+	+ moderate
	EA	+	ND	ND	-	-	+	-
Outcome of pregnancy		TOP at 29+5 WG	TOP at 13 WG	ND	/	/	TOP at 21 WG	TOP at 30 WA
Fetal autopsy additional data		Proximally placed thumbs, dysplastic ears , EA type C, micrognathia, microcephaly, malar hypoplasia	Non fetal autopsy		Live-born PMR (1 year)	Live-born PMR (6 years)	Proximally placed thumbs, low-set dysplastic ears, microtia, severe micrognathia, cleft palate, EA	Normocephaly, downward slanting eyes, low-set dysplastic round ears, hypoplastic lobules, short neck, micrognathia, posterior cleft palate, proximal placed right thumb
Family history		Their mother had microcephaly, mild ID, brachydactyly, mixed hearing loss		ND	-	-	-	-
Diagnosis's term of first sign		29 WG	13 WG	27 WG	32+3 WG	15+2 WG	12 WG (cleft palate)	22+3 WA
Genetic analysis		c.2823+1del, splicing in intron 27 of *EFTUD2*, inherited from the mother		*EFTUD2* variant	*EFTUD2* variant	*EFTUD2* variant	c.1058+1G>A, splicing in intron 12 of *EFTUD2, de novo*	c.2046-1G>T, splicing in intron 20 of *EFTUD2*

Abbreviations: US: Ultrasound examination, SGA: Small for gestational age, IUGR: Intrauterine growth retardation, SD: standard deviation, ND, Not determined, CNS: Cerebral Nervous System, EA: Esophageal atresia, PMR: Psychomotor retardation, ID: Intellectual disability, WG: weeks of gestation, WA: weeks of amenorrhea, TOP: Termination of pregnancy

3. Discussion

Mandibulofacial Dysostosis with Microcephaly, Guion-Almeida type (MFDGA) (OMIM #610536) is a rare genetic disorder described for the first time by Guion-Almeida et al in 2006 [1]. This syndrome is characterized by congenital or postnatal microcephaly (89%), and dysmorphic features due to first and second branchial arch anomalies [2], including malar and mandibular hypoplasia (93%), palate clefting (38%), dysplastic ears (98%) and hearing loss (77%) [3,4]. Major extracranial malformations include esophageal atresia (41%) and congenital heart disease (40%) [4]. Thumbs abnormalities are reported in 25% of cases, that is why some authors reclassified MFDGA as one of a preaxial acrofacial dysostosis group [2]. Short stature is present in approximatively one third of individuals and intrauterine growth retardation (IUGR) is also reported [4]. Intellectual disability (mild, moderate, or severe) is reported in 97% of cases [3-5].

In 2012, haploinsufficiency of the EFTUD2 gene was identified as the causative mechanism of MFDGA through whole exome se-

quencing of four individuals having the same distinctive mandibulofacial dysostosis [3]. The Elongation Factor Tu GTP binding domain containing 2 or EFTUD2 gene is localized on chromosome 17 at 17q21.31. It encodes for the U5 small nuclear ribonucleoprotein particle (snRNP), which is one component of the major spliceosome that mediate intron splicing [3,6,7]. Therefore, shortage of this protein impairs mRNA processing.

MFDGA is a highly penetrant but variably expressive autosomal dominant syndrome [4]. Most of affected individuals (75%) have a de novo heterozygous EFTUD2 pathogenic variant [6,8,9].

Lines et al [3] had identified the major postnatal criteria of MFDGA that Williams et al [10] have reused in table 1. All these signs could variably overlap with other craniofacial disorders such as CHARGE, Goldenhar, Nager, Feingold and Treacher Collins syndromes [2,11-13]. To the best of our knowledge, no MFDGA prenatal diagnosis criteria have been previously established, but several of postnatal signs could be antenatally seen if specifically, and carefully searched. Thereby, when the diagnosis is strongly suspected, molecular analysis of EFTUD2 could be proposed.

In table 2, we collected, in addition to our case, prenatal findings of 6 other fetuses with MFDGA syndrome previously reported in literature [5,8,14,15]. Unfortunately, the cohort is small, and a lot of data is missing that could be related to limitations of the ultrasound examination and the term of pregnancy the US and TOP were done. However, Table 2 shows that MFDGA should be evocated in presence of micrognathia (4/5) and cleft palate (3/5). If these signs are detected, detailed US examination by an experimented practitioner is recommended to carefully examine the size and position of the ears, presence of enchondroma or thumbs anomalies. Microcephaly is seen in 89% of MFDGA cases in literature [4]. The onset is more often prenatal (76%) but can be postnatal in some cases. In our series, prenatal microcephaly was found in 1/6 of cases. The presence of microcephaly and/or IUGR, might help the diagnosis of MFDGA in prenatal situation, considering that they are not common in Nager or CHARGE syndrome [2,8].

Although US examination and MRI reveal a structurally normal brain in most of postnatally reported cases of MFDGA [4] (apart from microcephaly), central nervous system (CNS) malformations were observed in 5/7 antenatally reported fetuses. This sign, that is not part of major postnatal criteria, should be included in prenatal situation. It is possible that most fetuses with MFDGA with severe brain abnormalities prenatally detected might be interrupted without prenatal or postmortem diagnosis.

If diagnosis of MFDGA is evoked prenatally on US examination, we should propose third trimester fetal brain MRI and prenatal genetic analysis, by analyzing the DNA extracted from fetal cells. CGH-array should be the first-tier diagnostic test since approximately 16% of reported cases of MFDGA are caused by chromosomal deletions [9]. If CGH-array is normal, EFTUD2 screening or exome sequencing, if available, could be proposed.

Prenatal diagnosis of MFDGA is a difficult task considering the absence of specific US signs. The warning signs accessible in a routine US examination are hydramnios, cerebral abnormalities (biometric or morphological) and retrognathia. When present, finer and more specific signs such as esophageal atresia, posterior palate cleft, abnormalities of the ears should be looked for.

We present herein an additional prenatal case description of MFDGA. Although several signs can be detected by US examination, the diagnosis remains difficult in prenatal period. From the literature, MFDGA is rarely evoked or confirmed prenatally. In the most of antenatally cases, the signs observed were serious enough for the couple to opt for termination of pregnancy, notably NCS malformation. Since there are few descriptions in the literature of prenatal findings in MFDGA, we hope that our report will contribute to the prenatal ultrasound recognition of this condition.

References

1. Guion-almeida ML, Zechi-ceide RM, Vendramini S. A new syndrome with growth and mental retardation , mandibulofacial dysostosis , microcephaly , and cleft palate and Alfredo Tabith Ju. Clin Dysmorphol. 2006; 15:171-4.
2. Wieczorek D. Human facial dysostoses. Clin Genet. 2013; 83: 499-510.
3. Lines MA, Huang L, Schwartzentruber J, Douglas SL, Lynch DC, Beaulieu C, et al. Haploinsufficiency of a Spliceosomal GTPase Encoded by EFTUD2 Causes Mandibulofacial Dysostosis with Microcephaly. Am J Hum Genet. 2012; 90: 369-77.
4. Lines M, Taila Hartley, Boycott KM. Mandibulofacial Dysostosis with Microcephaly. Genereviews. 2014; 1-18.
5. Gordon CT, Petit F, Oufadem M, Decaestecker C, Jourdain A, Andrieux J, et al. EFTUD2 haploinsuf fi ciency leads to syndromic oesophageal atresia. J med Genet. 2012; 24: 737-46.
6. Lijia Huang, Vanstone MR, Hartley T, Osmond M, Barrowman N. Mandibulofacial Dysostosis with Microcephaly: Mutation and Database Update. Hum Mutat. 2016; 37(2): 148-54.
7. Fabrizio P, Laggerbauer B, Lane WS, Luhrmann R. An evolutionarily conserved U5 snRNP-specific protein is a GTP-binding factor closely related to the ribosomal translocase EF-2. EMBO J. 1997; 16(13): 4092-106.
8. Lehalle D, Gordon CT, Oufadem M, Boutaud L, Baumann C, Boute-benejean O, et al. Delineation of EFTUD2 Haploinsufficiency-Related Phenotypes Through a Series of 36 Patients. Hum Mutat. 2014; 35(4): 478-85.
9. Gandomi SK, Parra M, Reeves D, Yap V, Array-cgh GC. Array-CGH is an effective first-tier diagnostic test for EFTUD2 -associated congenital mandibulofacial dysostosis with microcephaly. Clincal Genet. 2015; 87: 80-4.
10. Williams LA, Quinonez SC, Uhlmann WR. The Genetics Journey : A Case Report of a Genetic Diagnosis Made 30 Years Later. J Genet Couns. 2017.

11. Meizner I, Carmi R, Katz M. Prenatal Ultrasonic Diagnosis of Mandibulofacial Dysostosis (Treacher Collins Syndrome). J Clin Ultrasound. 1991; 19(February):124-7.

12. Lacour JC, Mcbride L, Hilaire HS, Mundinger GS, Moses M, Koon J, et al. Novel De Novo EFTUD2 Mutations in 2 Cases With MFDM , Initially Suspected to Have Alternative Craniofacial Diagnoses. Cleft Palate-Craniofacial J. 2019; 56(5):1-5.

13. Nicolaides KH, Johansson D, Donnai D, Rodeck CH. PRENATAL DIAGNOSIS OF MANDIBULOFACIAL DYSOSTOSIS. Prenat Diagn. 1984; 4(November 1983):201-5.

14. Mouthon L, Busa T, Bretelle F, Chantal HK, Nicole M, Sigaudy S. Prenatal diagnosis of micrognathia in 41 fetuses : Retrospective analysis of outcome and genetic etiologies. Am J Med Genet A. 2019; 179(12):1-9.

15. Xu B, Zhen L, Li D. First-trimester detection of micrognathia as a presentation of mandibulofacial dysostosis with microcephaly. J Obstet Gynaecol (Lahore) [Internet]. 2021; 41(5): 821-823.