

A CLINICAL STUDY OF 31 INDIVIDUALS WITH MIDLINE FACIAL DEFECTS WITH HYPERTELORISM AND A GUIDELINE FOR FOLLOW-UP

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ABSTRACT - In order to contribute to clinical delineation of midline facial defects with hypertelorism (MFDH) and to etiologic diagnosis of the isolated form, 31 patients with MFDH unaffected by known syndromic associations were evaluated. Group A included patients personally examined by the authors, while Group B included those previously evaluated by other geneticists. Among the 14 patients from Group A, there were 7 with distinct pictures of multiple congenital anomalies. In Group B, 5 of the 17 patients also exhibited a distinct pattern of defects. Among isolated MFDH, there was association with anomalies of the skull and facial bones (13/14), otorhinologic (11/16), central nervous system (9/16), and ocular (6/7), and audiologic (3/16); 1/3 of the cases had a relevant gestational intercurrents. Isolated FNM may have involvement of environmental components in some cases; the possibility of a syndromic picture should be extensive investigated. Follow-up of such patients must include the examinations herein performed.

KEY WORDS: craniofacial anomalies, facial clefts, ocular hypertelorism, frontonasal dysplasia, frontonasal process, follow-up.

Estudo clínico de 31 indivíduos com defeitos de linha média facial com hipertelorismo e diretrizes para seguimento clínico

RESUMO - Objetivando contribuir com o delineamento clínico de defeitos de linha média facial com hipertelorismo (DLMFH) e com o diagnóstico etiológico das formas isoladas, foram avaliados 31 indivíduos com DLMFH sem condições clínicas definidas. O Grupo A constituiu-se de pacientes examinados pessoalmente e o Grupo B, inicialmente, por outro geneticista. Entre os 14 pacientes do Grupo A, detectou-se 7 novos quadros de anomalias múltiplas (AM). No Grupo B, 5 dos 17 pacientes exibiram um quadro clínico único e peculiar. Nos casos de DLMFH isolados, detectou-se associação com anomalias de ossos de crânio e face (13/14), otorrinolaringológicas (11/16), de sistema nervoso central (9/16), oculares (6/7), e audiológicas (3/16); houve antecedentes gestacionais relevantes em 1/3. Existem evidências de envolvimento de fatores ambientais em parte dos casos de formas isoladas de DLMFH, devendo-se atentar para a possibilidade de um quadro distinto de AM. Todas as investigações realizadas são úteis para avaliação e seguimento clínico.

PALAVRAS-CHAVE: anomalias craniofaciais, fendas faciais, hipertelorismo, displasia frontonasal, processo frontonasal, seguimento clínico.

Midline facial defects with hypertelorism (MFDH) is the name suggested for a rare and heterogeneous group of craniofacial disorders mainly characterized by ocular hypertelorism and bifid nose. Several denominations have been used for this condition, such as *median cleft face syndrome*¹, *frontonasal syndrome*², *frontonasal dysostosis*³, and *malformative frontonasal sequence*⁴. *Frontonasal dysplasia*⁵ is the name most commonly accepted; however, after a critical review of this clinical condition based upon dysmorphology concepts the same authors proposed

the denomination *frontonasal malformation*⁶. The existence of different denominations can be easily attributed to the clinical complexity of this condition, which has been described from different points of view, according to the professional experience of each author. Considering all these particularities, the descriptive name herein proposed (MFDH) could be a real possibility of an integrative denomination for different health professionals. In the future, it could facilitate the descriptions concerning this heterogeneous group. Besides differences among denomina-

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tions, pathogenesis is still incompletely understood. Failure of formation of the nasal capsule during embryogenesis, abnormalities on mesenchymal migration from neural crest cells and unbalanced blood flow to the frontonasal process region could be implicated in causation of this condition⁷. Clinical classification of facial clefts varies from those based upon clinical and radiological data^{1,8}, or involving embryological aspects^{5,9}. There is also a specific facial classification for frontonasal dysplasia⁵, but is seldom mentioned.

In view of the clinical variability of MFDH, current classification and diagnostic criteria are still not appropriated. Different diagnostic criteria are mentioned, with some overlapping between them. Affected individuals should have two or more of the following features: true ocular hypertelorism, broadening of nasal root, median face cleft affecting the nose or both nose and upper lip and, at times, the palate, unilateral or bilateral clefting of the alae nasi, lack of formation of the nasal tip, and anterior cranium bifidum⁶. Another classification considered ocular hypertelorism, broad nasal root, and variable degree of median nasal groove as the main diagnostic signs¹⁰. After extensive review¹¹, it was suggested that a diagnosis of MFDH should be made for individuals presenting ocular hypertelorism (which leads to broadening of the nasal root) and medial and (or) lateral nasal cleft. These authors also suggest that the use of these criteria could lead to better knowledge of this anomaly and the need for a new classification.

Clinical presentation of MFDH includes isolated cases as well as those in which it is part of syndromes with different etiologies, such as craniofrontonasal dysplasia^{12,13}, acromelic frontonasal dysplasia¹⁴, and oculofrontonasal spectrum^{15,16}.

The rarity of isolated cases, the different terminologies, classifications and emphasis in the reports, as well as the absence of detailed clinical and familial history do not allow enough insight into the real etiologic and clinical profile of MFDH.

Despite that, it is known that there is no deviation of sex ratio, and most cases are sporadic. In view of its rarity, it is not possible to verify the existence of racial variability on prevalence or incidence. Heritability also could not be established, as the few reported cases of twinning belong to different populations and times. Chromosomal aberrations are rarely reported¹⁷⁻²⁰. A submicroscopic deletion of 22q11 was observed in a particular group presenting MFDH and tetralogy of Fallot²¹. In 2 patients presenting a

nasal dimple and 22q11.2 microdeletion, it was suggested that this picture should not be confused with the nasal abnormalities seen in frontonasal dysplasia²². After careful review, familial recurrence of the isolated form could be characterized in just two families^{23,24}, but it was not possible to distinguish between an autosomal dominant or X-linked pattern of inheritance.

The aims of this study were to establish the main clinical features of MFDH and to identify the main etiological factors related to isolated MFDH.

METHOD

The group was obtained from May, 1992 to November, 1996, and most of the individuals have been followed since then. It was composed by 31 individuals with MFDH (17F, 14 M) whose ages varied from 2 months to 29 years, selected through pictures and medical records from the Department of Medical Genetics / FCM / UNICAMP and specialized craniofacial hospitals.

Inclusion criteria were ocular hypertelorism with median and (or) lateral nasal cleft; patients with well-known syndromes were excluded (Figs 1,2,3,4). Group A was composed of 14 individuals personally examined by the first author, while sample B included those previously evaluated by another clinical geneticist with expertise on craniofacial anomalies. After that, they were evaluated by one of the authors (VLGSL) through pictures and clinical examination (17 individuals).

Procedures – Patients in group A were evaluated by a specific investigation protocol including clinical history and dysmorphologic examination and, whenever possible, skull and facial X-rays, computerized tomography of brain, ophthalmologic and otorhinologic evaluation and GTG banding karyotype. Medical records were reviewed for complementary informations about Group B. A dysmorphological approach was performed for elucidation of diagnosis in all cases.

Based upon clinical evaluation, patients from each group were considered to be isolated (or associated with non-specific clinical signs) (samples A₁ e B₁) or associated with multiple congenital anomalies involving different development fields (samples A₂ e B₂).

Data from groups A₁ and B₁ were compared by t test, chi-square test and Fisher's test. Syndromic pictures which could be characterized in samples A₂ and B₂ during this study were described.

This study was approved by the Research Ethics Committee (protocol number 488/2002).

RESULTS

All variables herein mentioned were compared between the groups A₁ and B₁. Considering that there was no statistical difference between them, they were described as a whole. Among 19 individuals (8M:11F), the sex ratio in this sample did not

deviate significantly from 1:1, mean maternal age was 28.4 years (SD=5.9), mean paternal age was 31.6 years (SD=7.3) and mean inbreeding coefficient was 0.00082; 1 case of discordant twinning was recognized.

Problems during gestation were mentioned in 12/18, including epilepsy (1/18), alcohol ingestion (1/18), hyperemesis (1/18), symptomatic myomatosis (1/18), bleeding (2/18), twinning (1/18), oral anticonceptual use (2/18), unspecified "poison" ingestion (1/18), hypothyroidism (1/18) and "abnormal" pregnancy (1/8).

There was no evidence of intrauterine growth retardation (mean birth weight: 3.1 kg; SD= 0.6). There were no abnormalities of anthropometric data at different ages in comparison with normal patterns, as well as in neurological development, according to information given by the families. Learning disabilities were mentioned in 3/9 individuals who were more than 7 years old.

Bone abnormalities in skull / facial X-rays were detected in 11/12. When bone abnormalities which could only be detectable by computerized tomography (CT) of skull and face are added, 13/14 individuals had some abnormality in these evaluations.

Considering central nervous system (CNS) abnormalities, CT was abnormal in 9/16, including *corpus callosum* anomalies (6/16) (lipoma 2/16, agenesis 1/16, dysgenesis 2/16); encephalocele (2/16) and complex CNS abnormality (1/16); in another case, an ethmoidal encephalocele was suspected.

Otorhinologic abnormalities were found in 11/16; in 5 cases, anomalies could only be detected by a specialist; audiometric abnormalities were observed in 3/14.

Ophthalmic findings were described in 6/7, with predominance of strabismus (3/7) and partial lens opacity (2/7); in one case there were severe abnormalities of palpebral fissures, extrinsic eye muscles and lachrymal ducts.

Table. Clinical description of patients studied.

Sex	Main clinical findings	Pattern of transmission	Denomination proposed	Reference
Group A₂				
Male	Mental retardation, coronal craniosynostosis, alar and lip/palate clefts, nystagmus, corneal leukoma, cataract, severe visual loss	? Isolated case	Crânio-oculo-fronto-nasal malformation	Gil-da-Silva-Lopes, et al, 1997
2 Female	Mental retardation, MFDH, Fissure / dysgenesis of <i>corpus callosum</i> , extensive mongolian spots, rugose <i>labia majora</i> , Hypoplastic <i>labia minora</i> Anteriorized anus, Precocious pubarche*, Pyelocalyceal duplication **	? Unrelated cases	MFDH <i>corpus callosum</i> anomalies, extensive mongolian spots and mild ano-genital abnormalities	Still in follow-up, unpublished data
2 Female	MFDH, Hypoplastic <i>labia majora</i> , abnormal implantation of clitoris, asymmetric lower limbs, dislocation of hips ***, bone cyst in femur **, Neuromotor delay ****	AD? Mother and daughter	FNM, mild ano-genital anomalies and skeletal alterations	Still in follow-up, unpublished data
Male	MFDH, Pre / post natal macrosomia, normal bone age, prominent ears, blepharoptosis, epicanthus and strabismus, bifid uvula, dental exfoliation, inguinal hernia, hypospadias, hypotonia, neuropsychomotor delay, <i>cafe-au-lait</i> spots	? Isolated case	Midline defects, macrosomia, mental retardation and dental abnormalities	Still in follow-up, unpublished data
Male	MFDH, narrow and anteverted nostrils, bifid uvula, atrial sept defect, aortic stenosis, diaphragmatic hernia, abnormal vertebra, peno-scrotal inversion, normal intelligence	? Isolated case	Midline defects, ocular abnormalities and normal intelligence	Still in follow-up, unpublished data
Group B₂				
4 Male and 1 Female	MFDH, median cleft lip, blepharoptosis, agenesis / dysgenesis of the corpus callosum, basal encephalocele, "mild neuropsychomotor delay" (?) #	? Unrelated cases	Frontonasal dysplasia with optic disc abnormalities and other midline craniofacial defects	Lees et al., 1998; Richieri-Costa and Guion-Almeida, 2004

*Case 1; **Case 2; ***Present in the mother; ****Present in daughter; AD, autosomal dominant; #cases previously diagnosed by craniofacial dysmorphologist.



Figure. Individuals presenting MFDH. Note the clinical variability.

Chromosomal analyses on GTG banding were normal in 14 / 14 individuals.

Table presents the main clinical features of patients with undescribed syndrome pictures (Figure) which were identified in this sample (groups A₂ and B₂).

DISCUSSION

Although there are some important papers about MFDH^{1,5,6,25}, as well as an interesting review about this condition from a rhinologic perspective²⁶, this seems to be the first report of a large sample of MFDH in which the patients were selected using homogeneous diagnostic criteria. A careful dysmorphic evaluation allowed delineation of 5 pictures of multiple congenital anomalies in group A. In six of them, after extensive search in the literature, the authors decided to maintain the follow-up before any conclusion; during this study, one case were published by the authors, as a new condition²⁷. In group B, 5 individuals presented MFDH associated with median cleft lip, blepharoptosis, agenesis / dysgenesis of the corpus callosum, basal encephalocele and mild neuropsychomotor delay. This clinical picture has some similarity with others previously described^{28,29}, but they are still on genetics investigation.

There were neither familial recurrence nor chromosome aberrations which could be diagnosed with usual cytogenetic techniques. The mean inbreeding coefficient of this sample was lower than that estimated for the Brazilian population (0.001), and maternal and paternal age average were also not different from that observed in the Brazilian population by the same authors (maternal age: 25.49 years, SD=6.43; paternal age: 30.20 years, SD=8.67)³⁰. These data did not indicate a genetic etiology (chromosomal, monogenic or polygenic) for MFDH in this sample.

Unfortunately, the finding of only one pair of discordant twins of unknown zygosity did not allow an estimate of the heritability of MFDH. However, it is interesting to point out that craniofacial anomalies in general (caused by either malformation or deformation) seem to be more frequent in monozygotic twins³¹. It was also suggested that twinning, *per se*, could be considered a congenital malformation³².

Cohen et al.³³ affirmed that the frequency of twinning in families with a case of MFDH would be higher than that of the general population, which could not be verified in this study. The authors commented that some clinicians imagined that anomalies of the frontonasal process could be the result from an incomplete twinning of the head. However, considering that this defect is caused by anterior duplication of the notochord, it would be possible supposed that a mildest form would result on the duplication of the hypophysis, and, in the most severe case, diprosopia. As there was no evidence of this spectrum of anomalies in MFDH, this hypothesis would not be supported. In fact, there was a unique description of a hypophyseal duplication in a MFDH³⁴.

MFDH was described in discordant dizygotic twins by some authors^{1,35-38}. Discordant monozygotic twins were also described^{1,37}. Brazilian concordant monozygotic twins were described³⁹. We observed that 2/3 of the nonsyndromic MFDH individuals had a history of gestational problems, which can be considered relevant in 1/3. In these cases, the possibility of an environmental influence may be considered, especially in view of the recognized external influence on developmental genes activities. Unfortunately, information was not detailed enough to allow definite conclusions. One of the patients was exposed to high doses of alcohol during gestation. Interestingly, craniofacial and CNS manifestations in fetal alcohol

syndrome, in which some of the facial findings resemble MFDH had been reported⁴⁰.

Most secondary anomalies associated with non-syndromic MFDH involved the midline, reinforcing the hypothesis of a developmental field defect^{4,6}.

A history of developmental delay was not detected in this study. However, interesting results, mainly involving cerebellar features, were obtained using a specific neurological protocol⁴¹. Learning disabilities, which were detected in 1/3 of MFDH individuals, could be due to an intrinsic mental impairment, complicated by low vision and hearing loss. Self – image disturbances are also a problem in the social life of an individual with craniofacial anomaly⁴²⁻⁴⁴. A specific study still in course about neuropsychological and neurological aspects in MFDH has been conducted by our group and preliminary results showed a heterogeneous but important correlation between them, reinforcing the idea of an intrinsic CNS abnormality in this condition (*unpublished data*).

Complementary evaluations indicated the association of MFDH with skull and facial bone abnormalities (13/14), as well as CNS defects (9/16). Facial bone defects could be explained based upon disturbance of the embryonic development of the nasal capsule and the frontonasal process⁴⁵.

Abnormalities of corpus callosum, particularly lipomas and calcification, are the most common CNS defect associated with MFDH^{1,37,42}; the angular analysis of corpus callosum of MFDH individuals suggested that positional anomalies of this structure are intrinsically related to this condition⁴⁶. The advent of magnetic resonance image (MRI) brings new possibilities for a structural investigation. Using this technique, other structural abnormalities and errors of neuronal migration were detected in a large sample of MFDH individuals⁴⁷. In syndrome patients, MFDH was described in association with bilateral periventricular nodular heterotopia and mental retardation⁴⁸ and with multiple pericallosal lipomas in 2 siblings⁴⁹.

Ophthalmic (6/7) and otorhinologic (11/16) abnormalities were also important findings, and audiometric problems were less common. An isolated case of MFDH with optic nerve colobomata and nystagmus was reported⁵⁰. In 1994, 9 individuals affected by MFDH were evaluated before surgical procedures. Two had mild facial defects, and refraction errors, strabismus and amblyopia. In 7 patients with severe facial involvement, 71% had significant refraction errors, 51% had strabismus and 27% severe structural ocular anomalies. The authors conclude that the high

incidence of strabismus could be associated with difficulties of ocular accommodation related to ocular hypertelorism⁵¹. These findings are very similar to the sample herein described, except for the frequency of severe refraction errors, and they indicate that a complete ophthalmic evaluation should be part of routine investigation of MFDH.

Audiometric findings have not been securely documented until now. About 30% of MFDH patients evaluated, including syndromic and isolated cases, had hearing loss 51. In our study, this feature was detected in 1/5 of cases, which indicates that audiometric examination and otorhinologic evaluation should always be done.

In conclusion, in order to establish guidelines for follow-up of MFDH, considering that MFDH is often part of a syndromic picture, this fact should be taken into account during clinical evaluation. Isolated MFDH is usually associated with skeletal abnormalities of the *cranium* and face, as well as anomalies of CNS, and ophthalmic and otorhinologic abnormalities. Considering these findings, evaluation and clinical follow-up of a patient with MFDH should be multidisciplinary and include: skull and facial X-rays, computerized tomography / MRI of the *cranium*, and ophthalmic, otorhinologic and audiometric evaluation.

Finally, in view of etiological heterogeneity of isolated MFDH, an appropriated and detailed clinical description, high resolution chromosomal analysis and other techniques, including studies of mutations on developmental genes in affected individuals, may add more information in some cases.

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