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ORIGINAL RESEARCH

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Moebius syndrome: Craniofacial clinical manifestations and their association with prenatal exposure to misoprostol

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Abstract

Background: A growing link between prenatal exposure to misoprostol (PEM) and Moebius syndrome (MS) or sequence has been reported. Our objectives were to describe the craniofacial clinical manifestations associated with MS and to determine the frequency of PEM, comparing cases of exposure and nonexposure.

Methods: A descriptive, cross-sectional study of 140 patients with MS. Clinical evaluations, as well as 140 interviews with mothers residing in 39 cities or districts of Colombia, were carried out between April 2008 and May 2018. Additionally, previous clinical history of each case was reviewed.

Results: The average age of the patients with MS was 8.4 years (29 days to 48 years). All of them presented facial nerve involvement and abducens, 112 (80.8%) with bilateral facial paralysis. 98.5% presented craniofacial disorders, and there were no significant differences between those exposed and not exposed to misoprostol. Forty-seven percentage of patients (64 cases) presented PEM, in 98.4% of which abortion had been intended.

Conclusion: PEM could have an influence in the appearance of new cases of MS by increasing the frequency of bleeding during gestation, without increasing the number of associated craniofacial malformations. We present the biggest series on MS and craniofacial findings in the literature, along with a meaningful reference for its understanding.

Level of Evidence: 3b.

KEYWORDS

abducens paralysis, craniofacial abnormalities, facial paralysis, failed abortion, misoprostol exposure, Moebius syndrome

1 | INTRODUCTION

Moebius syndrome (MS) or sequence is a rare congenital disease described for the first time in Germany, by Von Graefe in 1880,[1]

The preliminary results of this work were presented at the XXVI Pan-American Congress of Otorhinolaryngology and Head and Neck Surgery, Cartagena, Colombia, 26-29 October 2014. The definitive results of this work were approved for presentation at the World Congress of Pediatric Otolaryngology (*Paper No 4619*), Buenos Aires, Argentina, 7-10 April 2019.

Harlan in 1881,[2] and Moebius in 1888 and 1892.[3,4] It is characterized by nonprogressive facial and ocular abduction paralysis, caused by impairment to the facial (cranial VII) and abducens (cranial VI) nerves, respectively. It can be associated with various craniofacial and orolingual defects and malformations, as well as to impairment of other cranial nerves (CN).

There is little epidemiological data on the incidence and prevalence of MS. In the Dutch population, its incidence has been estimated at 0.002% (4 in every 189 000 births).[5] In the United States, its frequency has been calculated as 0.002% to 0.0002%, with an incidence of 1/50 000 recent births.[6] In Spain, its prevalence is between 1/490 000 and 1/677 000 inhabitants and its incidence is 1/115 000 live births (around 3 or 4 new cases each year).[7]

The etiology of MS is not clear. It has been described, on one hand, as a *genetic* etiology associated with abnormal development of the rhombencephalon[5]; and on the other hand, as a *vascular* etiology associated with ischemic damage caused by interruption of blood flow in the brain stem during a critical period of embryogenesis, affecting the areas of the basilar, subclavian or vertebral arteries, or their tributary arteries or embryonic precedents.[8,9] Ischemic events can be associated and/or triggered by environmental or mechanical factors present in the 4th to 12th weeks of gestation, with the use of cocaine,[10,11] ergotamine,[12] thalidomide,[13] benzodiazepines,[14] mifepristone,[15] and misoprostol having been reported. Studies carried out in Brazil have presented evidence suggesting a strong connection between prenatal exposure to misoprostol (PEM) and a greater occurrence of defects caused by vascular disruption and congenital malformations, particularly MS.[16-21]

2 | MATERIALS AND METHODS

2.1 | Study design

A descriptive, transversal study of a sample of 140 MS cases from the register of the Moebius Foundation of Colombia (FNMC) and the Moebius Art Project of Colombia. These were identified and evaluated over a period of 10 years, from April 2008 to May 2018, and all met the minimum diagnostic criteria (MDC) ratified in the Scientific Conference on Moebius Syndrome in Bethesda, Maryland, USA in 2007 (congenital, nonprogressive uni- or bilateral facial paralysis associated with a deficiency in ocular abduction).[22] The exclusion criteria were congenital myopathy, facial paralysis with an obstetric cause, and congenital facial paralysis without paralysis of the abducens nerve.

All medical evaluations with the patients and interviews with the mothers were carried out by one doctor, some with photographic, audio, or video recording. The medical information was recorded in the first protocol, in the second the mothers' information was recorded, and in the third confidential protocol the mothers' responses regarding PEM in the first trimester of gestation (FTG) were recorded.

Participants resident in or near the city of Medellin (Colombia) were evaluated in the care area of the Neurosciences Group of Antioquia (GNA), while those participants resident in other cities and districts were contacted by phone to arrange an appointment, and the researchers traveled to each city or district to carry out the evaluations of the patients, along with their clinical histories and the interview with the mothers. The medical evaluation and clinical history lasted approximately 3 hours per participant and the interview with each mother lasted 2 hours.

2.2 | Ethical considerations

This study is part of the research project "Clinical and cognitive characterization of a sample of patients with Moebius syndrome in Colombia," financed by the Committee for Research Development (CODI) of the UdeA (code 2573-8764). In addition, the informed consent was approved by the ethics committee of the Faculty of Medicine of the University of Antioquia in Medellin, Colombia (Act of approval 16 May 2013). The ethics committee recommended that the information recorded regarding PEM in the third protocol be completely anonymous (no personal data pertaining to the mothers or patients was recorded).

2.3 | Statistical analysis

Demographic and clinical characteristics were described according to their nature as follows: for the qualitative variables, with absolute and relative frequency (%); and for the quantitative variables, with measures of central tendency (mean and median) and dispersion (SD or interquartile range). All the analyses were carried out using IBM SPSS STATISTICS version 23.

3 | RESULTS

3.1 | Diagnosis of MS

All the patients met the MDC, 100% presenting impairments both to facial movements and to the eye abduction. Bilateral facial paralysis was presented in 112 cases (80.8%), with the upper part of the face, particularly the forehead, observed to be completely rigid and inexpressive. However, most of these patients presented very slight movements in the lower part of the face, particularly at the level of the chin.

3.2 | Findings

Table 1 shows the craniofacial and orolingual findings. Among the most frequent of these, appearing in 91.43% (128 cases), was impairment of other CN aside from VI and VII. Impairment to the hypoglossal nerve (CN XII) was presented in in 71.43% (100 cases). Ninety-nine percentages of these were associated with lingual

TABLE 1 Diagnostic and clinical characteristics of patients with MS

Characteristic	Frequency n = 140	(%)	Exposure to misoprostol # (%) n = 64	No exposure to misoprostol # (%) n = 76	*P* value
Gender					
Masculine	83	(59.29)	43 (67.19)	40 (52.63)	.081
Feminine	57	(40.71)	21 (32.81)	36 (47.37)	
Facial paralysis (VII PC)					
Bilateral	112	(80.8)	53 (82.81)	59 (77.63)	.445
Unilateral	28	(19.2)	11 (17.19)	17 (22.37)	.445
Abducens paralysis (VI PC)					
Bilateral	140	(100)	64 (100)	76 (100)	—
Orofacial anomalies[a]	138	(98.57)	63 (98.44)	75 (98.68)	.707
Paralysis of other cranial nerves (PCs)	128	(91.43)	56 (87.50)	72 (94.74)	.128
Telecanthus	127	(90.71)	61 (95.31)	66 (86.84)	.085
High-arched palate	101	(72.14)	46 (71.88)	55 (72.37)	.948
Fissured tongue	100	(71.43)	44 (68.75)	56 (73.68)	.520
Tongue atrophy/hypoplasia	99	(70.71)	44 (68.75)	55 (72.37)	.639
Retrognathia	74	(52.86)	38 (59.38)	36 (47.37)	.156
Lip hypoplasia	71	(50.71)	27 (42.19)	44 (57.89)	.064
Micrognathia	60	(42.86)	26 (40.63)	34 (44.74)	.624
Open mouth	54	(38.57)	25 (39.06)	29 (38.84)	.913
Excessive dribbling	29	(20.71)	16 (25.00)	13 (17.11)	.251
Microtia	24	(17.14)	12 (18.75)	12 (15.79)	.643
Cleft palate	21	(15.00)	9 (14.06)	12 (15.79)	.776
Lingual frenulum	14	(10.00)	7 (10.94)	7 (9.21)	.734
Bifid uvula	14	(10.00)	9 (14.06)	5 (6.58)	.141
Absence of external auditory canal	5	(3.57)	1 (1.56)	4 (5.26)	.240
Prognathism[a]	3	(2.14)	1 (1.56)	2 (2.63)	.565
Apophysis auricular region	2	(1.43)	1 (1.56)	1 (1.32)	.902
Sucking disorders	134	(95.71)	61 (95.31)	73 (96.05)	.575
Language development disorders[b]	112	(80.8)	56 (87.50)	56 (73.68)	.138
Swallowing disorders	110	(78.57)	51 (79.69)	59 (77.63)	.768
Hypotonia	99	(70.71)	44 (68.75)	55 (72.37)	.639
Oxygen requirement at birth	82	(58.57)	39 (60.94)	43 (56.58)	.602
History of pneumonia (up to 2 y)	75	(53.57)	36 (56.25)	39 (51.32)	.560
History of apnea	46	(32.86)	17 (26.56)	29 (38.16)	.146
Use of nasogastric tube	44	(31.43)	18 (28.13)	26 (34.21)	.440
Gastrostomy	22	(15.71)	7 (10.94)	15 (19.74)	.154

Abbreviation: MS, Moebius syndrome.
[a]Fisher's exact test.
[b]Four patients excluded.

atrophy or hypotrophy with impairment to movement, while more than half showed twitching in the neutral or resting position, and 48% presented lateral deviation of the tongue, which could indicate a unilateral impairment of this CN.

In the evaluation of CN VIII, there were records of auditory evoked potentials in 74 cases (58.8%). Of these, 11 (14.86%) showed deafness and prior recurring otitis media, two suppurative otitis media with difficult management, while one case required a bilateral cochlear implant at 4 years of age due to severe deafness.

Meanwhile, visual evoked potentials (VEP) were performed in 43 patients, which included those aged over 1 year, where the visual pathway was more mature. Of the 37 cases selected, impairment was reported in only one case, which occurred along with a hydrocephalus that caused intercranial hypertension. In this case, 6 months after the

insertion of a shunt for the hydrocephalus, the VEP follow-up was reported as normal. Spontaneous nystagmus was not presented in any case.

Over the past 2 years, those cases aged over 5 years with school attendance, corresponding to 43 patients, were given an odor perception test (I PC). Anosmia, cacosmia, or parosmia was not presented in any case, and all correctly identified the smell of vanilla, cinnamon, and lemon. In addition, these patients were asked to identify three flavors (salt, sweet, and sour). All were able quickly to identify the acidic flavor; however, they were slower and less certain in distinguishing between the sweet and salty flavors.

Assessment of sensitivity in the face (CN V) was evaluated in 93 cases. The patients were subjected to contact with smooth, rough, cold, lukewarm, hard, and soft surfaces. In 39.75% (33 cases), differences in perception were found between one side of the face and the other; 9 presented impairment to thermal sensitivity (cold and lukewarm); while 11 had impaired ability to distinguish between smooth and rough surfaces, and 13 between hard and soft surfaces (metal and rubber).

The same patients referred to above were additionally subjected to an evaluation of spinal muscular strength (CN XI). They were asked to raise their shoulders and subsequently force was applied to these. In 19 cases (22.89%), little resistance was presented, and in five cases resistance was presented in an asymmetric manner. Seventeen of these patients were less than 9 years of age, while the other two were aged 11 and 14. Palpebral ptosis was presented in 27 cases (19.28%), and was unilateral in 19 of these. This finding could be associated with damage to the oculomotor nerve (CN III).

All patients with dentition and open mouth presented caries and impairment to the dental enamel, while 84.8% of those with dentition and closed mouth presented these impairments. Microretrognathia union was presented in 44 cases (31.4%).

The secondary functional impairments observed are obvious and frequent from the first days of life. Sucking problems were the main cause of early hospitalization. This impairment was associated with swallowing problems. The degree of severity of this was variable, with use of a parenteral route for feeding being required in almost half the cases, and the use of supplementary oxygen at birth required in slightly over half. However, seven of these latter cases (8.5%) continued to require supplementary oxygen after the third year of life. Five cases presented significant *brain stem atrophy*, evidenced in neuroimaging studies. The infection most frequently found in these patients in the first stages of life was pneumonia, which was recurrent in the large majority of cases until the second year of life. During this study, 7 cases (5%) died, 6 due to pneumonia, 4 before reaching the age of 2, and 2 before the age of 3. The other case occurred at the age of 18 months due to respiratory failure with no prior history of infection.

Speech and language impairments were present in the majority of cases, with the complex mechanism of language affected to various degrees. This depended on factors such as the impairment of the various CN that affect language (VII, VIII, IX, X, XII), as well as other anatomical conditions such as impairment to the auricular, maxillary or mandibular region, lingual frenulum, or absence of external auditory canal. Eighty percentages of cases (112 cases) received or had access to language therapy; however, most did not attend therapy regularly due to problems with their health service or adverse economic factors.

3.3 | Prior use of misoprostol

The average age of the mothers at the moment of birth was 24.6 years (ranging from 13 to 44). One hundred and twelve out of 140 (80%) of the mothers reported uterine bleeding in the FTG, the most frequent cause of which was the use of misoprostol (61/112 cases, or 54.5%). All the mothers self-administered misoprostol with the aim of abortion, in insecure and clandestine conditions, except one mother who reported having been tricked by her partner into taking two misoprostol tablets. 59.4% of the mothers were completely unaware of misoprostol when using it. The average week of bleeding

TABLE 2 Characteristics of mothers of patients with MS

Characteristic	Frequency n = 140	(%)	Exposure to misoprostol # (%) n = 64	No exposure to misoprostol # (%) n = 76	*P* value
Average age (y)			23.9	25.2	
Type of birth					
Vaginal	74	(52.86)	35 (54.59)	39 (51.32)	.691
Cesarean	66	(47.14)	29 (45.31)	37 (48.68)	
Time of birth (wk)					
Full term (greater or equal to 37)	95	(67.86)	44 (68.75)	51 (67.11)	.836
Preterm	45	(32.14)	20 (31.25)	25 (32.89)	
Uterine bleeding in FTG					
Present	112	(80.8)	61 (95.31)	51 (67.11)	.000
Use of misoprostol in FTG	64	(45.71)			
Consanguinity between parents	0	(0)	0	0	

Abbreviations: FTG, first trimester of gestation; MS, Moebius syndrome.

was the sixth (6.68) (range between 4 and 12). Other less frequent causes of uterine bleeding in the FTG were placental problems, abdominal trauma, oral medicines, injectable substances, or electric shock (Table 2).

Slightly over half were born vaginally, of which 12 were operative births, 8 with forceps, and 4 with vacuum. The main indication for caesarean (39.4%, or 26 cases) was premature membrane rupture. No case presented consanguinity between the parents and no case with familial aggregation was observed.

4 | DISCUSSION

A possible bias in our study could be denial by some of the mothers interviewed of having used misoprostol with the aim of abortion, despite the fact that it was explained to them that this information would be recorded confidentially and anonymously. Another possible bias could be the exact record of the gestational age at the time of PEM, given that this depends on the accuracy of the mother's memory.

In 2007 in Bethesda, Maryland, experts in the field came together for the Scientific Conference on Moebius Syndrome, and defined the MDC as the presence of congenital, nonprogressive uni- or bilateral facial paralysis associated with a deficiency in abduction of one or both eyes. Thus, a unified diagnostic criterion was established, independently of the wide variety of clinical manifestations associated with MS that continue to be found.

Not all the case series reported to date include the MDC in their selection criteria, which in some cases is due to their having been reported prior to 2007. The biggest case series reported up to 2007, Pastuszak et al in 1998, reported 96 cases with MS, of which 20.9% (20/96) did not meet the MDC.[18] The biggest case series after 2007, MacKinnon et al in 2014, presented a similar situation, describing a series of 112 patients, of which 19% (21/112) did not meet the MDC since they presented deficiency in ocular abduction without facial paralysis, or facial paralysis with preserved eye abduction.[22] Other authors reported smaller case series, such as Fons-Estupiña et al, who reported 20 cases of which 25% did not have impairment to CN VI,[23] and Terzis et al, who reported 42 cases of which 26.7% did not have damage to CN VI, although this study classified those cases that did not meet the MDC into two groups named "MS-like" and "incomplete Moebius."[24] As a result of these reports, there has been confusion regarding the diagnosis of MS and each classification system proposed has tended to increase this confusion. Nonetheless, they have great relevance in terms of optimizing the analysis from different perspectives. The classification proposed by MacKinnon et al is relevant for future genetic studies, while Terzis et al classified the lesion pattern of the affected CN, which is relevant for surgical approaches and treatment. However, it is important to maintain the MDC ratified since 2007 as the unified diagnostic criterion for MS, thereby eliminating factors that could cause confusion.

Another point of discussion regarding MS is whether to classify it as a syndrome or a sequence. In studies in the literature, it is classified in both ways, and its classic description as "Moebius syndrome" has been gradually shifting to "Moebius sequence." This is because it is due to an initial impairment (deformity or disruption) and presents as a primary defect, agenesis, or lesion of the nuclei of CN VII and VI in the brain stem, causing facial paralysis and impairment of ocular abduction, respectively. However, MS can be present in isolation or as part of a more extensive polymalformative clinical picture arising after the initial event during fetal development, with a wide presentation of congenital anomalies and associated clinical manifestations. In a broad sense, this rare disease can be explained as a brain stem dysgenesis, which can be determined genetically or acquired during the first stages of neurogenesis, with greater susceptibility between the 4th and 12th weeks of gestation. In this sense, MS could be classified along with other syndromes such as those of Pierre Robin, Carey Fineman Ziter, Cogan, MS-like, and incomplete MS. All these are associated with dysfunction of brain stem structures during the fetal period, cranial nerve lesions (some specific to their diagnosis), and associated congenital malformations. The clinical presentation of these depends on the extent of the brain stem area affected, and they may have lesion patterns in common.

Although it has been reported for several decades that MS does not have a clear gender predilection, based on a detailed evaluation of previous studies, we found a slight tendency for affected individuals to be male. The proportion of cases of masculine sex was reported in Brazil by Pastuszak et al in 1998 as 56% (n = 96) and by Gonzales et al in the same year as 63% (n = 19); in Switzerland by Strömland et al in 2002 as 72% (n = 25)[25]; in the Netherlands by Verzijil in 2003 as 54% (n = 37); and in Spain by Fons-Estupiña in 2007 as 80% (n = 20) and by Pertierra et al in 2014 as 62.5% (n = 64).[26] Welschen, in Argentina, is the only study to find the opposite trend, reporting the proportion of cases of male sex as 41% (n = 26).[27] Our study is in accordance with the majority of previous studies, with the prevalent gender being masculine (59.29% of cases). However, further study is required further to substantiate this slight tendency. With regard to facial paralysis, in the majority of cases this was bilateral, which is also in accordance with previous studies.

With regard to the etiology of MS, which is not clear, we did not find alterations in the karyotype of the 91 patients involved in this study. These were normal in all cases, findings similar to those reported by MacKinnon et al, who found the karyotypes of all 88 cases with MS who met the MDC with preserved vertical gaze to be normal. The same findings were reported by Strömland et al and Fons-Estupiña in Europe, and by Gómez-Valencia et al in Latin America.[28] However, despite the fact that MS is associated with a sporadic condition without family history, in some isolated cases a genetic association related more to alterations to specific genes or families of genes, including translocation and deletion[29-37] has been described. This association is not possible to generalize, and requires more specific study than a karyotype. On the other hand, the vascular or ischemic etiology suggests an interruption to blood flow in the brain stem during a critical period of embryogenesis. In our study, we found that in 80.8% of cases, a history of uterine bleeding in the FTG was presented, use of misoprostrol (MP) being the most prevalent cause of

bleeding. Only three cases of PEM presented no bleeding during the FTG. The remaining 95.3% presented uterine bleeding and had used MP with the aim of terminating their pregnancy. Vargas et al carried out a multicentric study in Brazil of 93 cases and 297 controls, where they compared the frequency of prenatal use of misoprostol in mothers of children with vascular disruption defects, and a control group in which other kinds of defect had been diagnosed. PEM was identified in 34.4% of children diagnosed with vascular disruption, compared to 4.3% for the control group. Meanwhile, Pastuszak et al, also in Brazil, found an association of MS with PEM of 49%, a very similar result to that found in our Colombian population. In addition, we found that the frequency of uterine bleeding in mothers who had used misoprostol to be 8.8 times higher than in mothers who had not used misoprostol (odds ratio = 9.9, confidence interval = 2.8-34.9). These are statistically significant results of great importance, which support even further the possible vascular etiology of MS associated with environmental factors.

MS is part of a pattern of specific malformations associated with PEM during FTG with a common mechanism associated with a vascular disruption whose incidence is unknown, most of this information has been reported in the context of the illegal use of MP. There are very few previous studies describing craniofacial findings of MS and this is the first to compare in detail these findings associated with PEM in FTG.

5 | CONCLUSIONS

This is the first study on MS and craniofacial findings in Colombia, in which the biggest patient sample reported worldwide to date was identified. The results provide further evidence for a possible vascular etiology of MS associated with environmental factors, especially PEM. This association could be favoring the increase in recent births with MS due to early vascular disruption, by increasing the frequency of uterine bleeding during gestation, without increasing associated craniofacial malformations.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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