The Epidemiology of Moebius Syndrome

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Abstract

Background: The epidemiology of Moebius Syndrome is actually unknown. In the present study we have investigated the epidemiology of MBS in a well defined population over a precise geographical area.

Materials and Methods: Our University Hospital is the only national referral centre for the diagnosis and treatment of MBS. Participants to this cross sectional study are patients affected by MBS which have been periodically followed by our medical staff since 1998. Most of the patients were referred to our hospital by the Italian Association of Moebius Syndrome (AISMO). Demographic data necessary for our purposes were made available by AISMO database updated to April 2018. Subjects were assigned to the geographical macro-areas which are the ones conventionally used for surveys and epidemiological investigations by the Italian National Institute of Statistics. Rates and prevalence of the MBS cases were calculated referring to the last survey of the Italian population of 2018. Every study parameter was then calculated by reference to the whole country and to macro-area partition. Gender rate and the corresponding prevalence were calculated with respect to the weighted whole population and to the respective gender population. Chi-square (c 2) analysis was adopted to investigate possible differences among geographical regions and/or gender. A p value <0.05 was considered statistically significant.

Results: 164 out of 212 MBS patients satisfied our inclusion criteria. All cases were Caucasian and sporadic. The median age at diagnosis was 3.6 years (range: 0-55); this range was significantly reduced to 0-5 years (median age at diagnosis: 2.2 years) for patients evaluated after 2007. The birth prevalence calculated was 0.06 cases per 10,000 live births with an overall prevalence of 0.27/100000 without any gender or geographical predisposition.

Conclusions: The rate of MBS prevalence herein observed, rounded for possible underestimation, is 0.3/100000 people without any geographical difference in the distribution of the cases. According to our data, MBS must be considered a rare disease but not so rare as previously postulated by researchers on their personal basis.

Introduction

Moebius syndrome (MBS) is the most common congenital cranial dysinnervation disorder. Its clinical features are impaired ocular motility, lagophthalmos, and lack of facial expression; these features are related to congenital non-progressive 6th and 7th nerve palsies that typically affect newborns bilaterally. MBS is diagnosed according to the recent “Bethesda Diagnostic Criteria”, which also include extra-ophthalmological features, such as involvement of other cranial nerves and motor, orofacial, musculoskeletal, neurodevelopmental, and social problems.[1] Patients who do not meet these criteria must be labelled Moebius-like and be considered as having a separate disorder.

More than a century after the first description of the disease[2], the aetiology of MBS is still unclear; recent studies have postulated a multifactorial pathogenesis in which a foetal toxic exposure acts on a genetic predisposition responsible for vascular terminal instability and focal microcirculatory failure at the level of the lower brainstem.[3-5] However, it is not clear what causes these changes and why they specifically disrupt development of the 6th and 7th cranial nerve nuclei; even less is known about the causes of the extra-ophthalmological signs and symptoms associated with MBS (*e.g.*, lingual and palate dysfunction, hypoplasia of the hand, clubfoot, and thoracic abnormalities).

The exact incidence and prevalence of MBS are not clear; the syndrome is considered a “rare disease” affecting a very small number of people. Clinicians and researchers estimate that this condition affects 1 in 50,000 to 1 in 500,000 newborns, but this estimate is based only on their personal experience with MBS patients, with no epidemiological basis.[6-8] In a Dutch series, the estimated prevalence of MBS was 0.002% of births (4 per 189,000 newborns).[9]

The Orphanet Report Series, Rare Disease Collection 2019 reports the estimated prevalence\incidence per 100,000 as “unknown” with only 300 cases described in the literature.[10] Other epidemiological estimates of series reported worldwide are anecdotal, with no statistical basis. It is difficult to plan an epidemiological study of MBS for many reasons: 1) despite the new diagnostic criteria, the disease is often over- and misdiagnosed in newborns; 2) like many other rare diseases, MBS does not have a regional register from which to derive data for epidemiological purposes; 3) there are no referral centres that provide multidisciplinary care with consequent dispersion of cases; 4) few physicians have expertise in MBS and they may be difficult to reach; and 5) MBS is often considered shameful and relatives or affected people may “self-marginalise”.

This study reports the epidemiology of MBS in a well-defined population; furthermore, we investigated whether there are geographical differences in MBS incidence\prevalence to identify factors that may cause or contribute to its development.

Methods

Since 1998, the University Hospital of Parma has been identified by the Italian Association of Moebius Syndrome (AISMO, www.moebius-italia.it) and by the Regional Health Department as the only national referral centre for the diagnosis and treatment of patients with MBS (*e.g.*, a multidisciplinary approach treating conditions ranging from strabismus correction to smile surgery). This allowed us to contact and follow virtually all of the MBS patients living in Italy. Even MBS patients who have been offered medical care elsewhere are evaluated in our hospital in the diagnostic phase.

To be included in our analysis, each MBS case had to satisfy the “Bethesda Criteria” without any radiological or clinical evidence of further neurological impairment; patients who did not satisfy these diagnostic criteria fully were labelled Moebius-like and excluded from our analysis. Every MBS case was periodically evaluated by our multidisciplinary team of physicians, which includes an ophthalmologist (A.C.), a neonatologist or paediatrician, a speech therapist, an orthodontist, an orthopaedist (for children with clubfoot or finger anomalies), and a maxillofacial surgeon with expertise in smile surgery; the frequency of visits depended on the severity of the disease, usually ranging from 6 to 24 months. Each visit includes a comprehensive ophthalmological evaluation of extraocular motility and refraction under cycloplegia in paediatric cases. A detailed history is obtained at the first visit from relatives of each patient and updated every visit. All patients (or relatives if minors) have previously given the AISMO consent to use their demographic data for research purposes and statistical analysis.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee (No. 93/2019/OSS*/UNIPR/June 14, 2019).

Statistical analysis

The authors used data made available by AISMO to obtain the following information for each registered member: date of birth, date and age of diagnosis, gender, and place of provenance/residence. The subjects were assigned to the five geographical regions (*i.e.*, Northeast, Northwest, Central, South, and Islands) conventionally used for surveys and epidemiological investigations in Italy. Every study parameter was then calculated by reference to the entire country and each region. The rates and prevalence (number of cases per 100,000 people) of MBS were calculated referring to the 2018 Italian census performed by the National Institute of Statistics.[11] The rate and corresponding prevalence were calculated for the entire population and each gender (*i.e.*, affected males/Italian males; affected females/Italian females).

Chi-square (c^2) analysis was used to investigate possible differences among geographic regions and gender. For gender tests, unweighted (*i.e.*, each rate was weighted equally across regions, independently of the actual gender population in the corresponding region) and weighted (*i.e.*, each rate was scaled to the corresponding gender weight, according to the population density in each region) data were analysed. A *p*-value <0.05 was considered statistically significant.

Data Availability Statement

Availability of data herein utilized can be found at the following links: www.moebius-italia.it and www.istat.it

Results

Descriptive statistics

The AISMO register contained 231 subjects. Of these, 67 were excluded as they did not satisfy the “Bethesda Criteria” fully (59 subjects), were not Italian citizens (4 subjects), or had incomplete data (4 subjects). The remaining 164 MBS patients (73 men, 44.5%) were considered for the study and analysed for epidemiological purposes (Table 1). All patients were Caucasian. The median age at diagnosis was 3.6 (range 0–55) years; this range was reduced to 0–5 years (median age at diagnosis of 2.2 years) for patients who were evaluated after 2007. Figure 1 shows the newly recorded cases in the AISMO register based on the year of birth; a progressive increase in recorded cases is evident from 1998, when the AISMO register was established, with the new diagnoses peaking (16 cases) in 2005–2006 (coincidentally after the Consensus Conference on Moebius Syndrome, which produced the "Bethesda Criteria"). The birth prevalence calculated for the most recent data (in 2018) was 0.06 cases per 10,000 live births.

Statistical analysis

The relative rate of MBS in the Italian population was calculated for males and females in terms of the total number of patients diagnosed and separately for each region (Table 1). The rates were evenly distributed across the different regions, with the exception of the Northwest, where more cases were located (Figure 2). Moreover, in this region, the gender rate differed since there were 1.5-times more females than males (62.7% *vs*. 37.3%).

The difference in the rate in the Northwest was confirmed with reference to both the total population (P-MT: 0.12 *vs*. P-FT: 0.20) and the gender-based subdivisions (P-MM: 0.24 *vs*. P-FF: 0.39).

The MBS rate of the total population (*i.e.*, both males and females) subdivided into the five regions differed significantly ($p < 0.001$; c^2-test). To verify whether this result was due to the larger population in the Northwest, the data were weighted to account for the different populations in the five regions. This analysis involved weighted rate data (*i.e.*, data rescaled to the actual population in each region). After this adjustment, no statistical significance was observed.

Finally, a c^2-test for the separate sex rates was performed. The analysis of males confirmed that the distribution across different regions was similar (no statistical differences for both "unweighted" and "weighted" data over the male population in the different regions). The analysis of females showed a significant ($p < 0.001$) difference for "unweighted" data. However, this difference lost significance when "weighted" data over the female population in different regions were considered. An analysis of the total weighted population dataset showed no significant differences on comparing the five regions.

Discussion

This study examined the epidemiology of Moebius syndrome in a well-defined population over a precise geographical area, using definite diagnostic criteria for MBS. In our series, this disease affects males and females equally, supporting the evidence that MBS is not an inherited X- or Y-related disease, this is an important information to give when physicians are asked about the risk of a second child developing the disease. The non-hereditary nature of this disease is supported by the fact that all cases were sporadic in our series and most reported series. This observation is in line with the recent hypothesis that MBS has a multifactorial basis and genetic mechanisms play a minor role.[3-5,12]

We found that the overall prevalence of MBS was 0.27/100,000 newborns. We have rounded this value to 0.3/100,000 because a few cases of MBS may have been missed, as some consider this disease shameful and may escape medical notice (and the AISMO database), tending to "self-marginalise". Regardless, the prevalence observed in our study is much different from prevalences reported in different parts of the world. For example, in the Dutch series, Verzijl *et al*. estimated a prevalence of 0.002/100,000, which is 100-times rarer than the prevalence reported here; similar prevalences have been reported by physicians with expertise on MBS in the United States, Sweden, and Brazil, but without any epidemiological basis.[6-8] From our data, we can conclude that MBS is a rare disease, but not as rare as previously thought; this must be kept in mind when planning healthcare strategies aimed at reducing/ameliorating the social impact and morbidities related this disorder.

Another important consideration is that we found a uniform distribution of MBS cases in the five regions considered. These five regions were conceived by ISTAT, as people living in them have different social, economic, and working lifestyles, with different climates characterizing each region. As we did not identify a region with a higher prevalence of MBS cases, we can exclude environmental factors such as pollution, weather conditions such as intense cold or heat, and prolonged sun exposure during pregnancy as causative for MBS. It appears that the environment had little or no influence on the disease pathogenesis in our population. The only reported agent that significantly increased the risk of newborns being affected by MBS (by a factor of 30) is the use of misoprostol during the first trimester of pregnancy.[13] Misoprostol (a synthetic prostaglandin E analogue) is an illegal abortifacient widely used in Brazil and other countries in South and Central America. As misoprostol is not in use in Italy, our epidemiological data on MBS lack any pharmacological bias, at least as far as misoprostol is concerned.

In addition, the patients who were evaluated by our staff after 2007 had an earlier diagnosis than those born before 2007 (2.2 *vs*. 3.4 years) with a significant reduction in the range, which was lowered to between 0 and 5 years of age. This interesting finding likely resulted from the efforts made during the last two decades by international associations to increase knowledge of this disease; another explanation may be that our specialised medical staff can be contacted easily by relatives of affected newborns, thereby allowing an earlier diagnosis. An early diagnosis of MBS means that we can provide care for affected individuals at a young age. This can have extremely positive effects on the patients' quality of life by significantly reducing the behavioural and psychological problems related to MBS. For example, with an early diagnosis we can plan smile surgery at a preschool age or we can perform early strabismus surgery when needed, thereby improving visual performance and reducing the risk of amblyopia other than developing the ability to smile.

Conclusions

Our data increase the knowledge of MBS providing its exact epidemiology which may be particularly useful when devising medical policies regarding this rare disease. Most rare diseases are considered "orphans" with no effective treatment; people affected are more vulnerable psychologically, socially, economically, and culturally, as they usually have no response for their medical condition. These difficulties can be overcome and the efforts made by the scientific community can increase our knowledge and give new hope for future treatments of this disorder.

Abbreviations

MBS= Moebius Syndrome, AISMO= Italian Association of Moebius Syndrome AISMO.

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Declarations

Ethics approval: As stated in the method section, "This study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee (No. 93/2019/OSS*/UNIPR/June 14, 2019)."

Consent for publication: This study does not contain any individual person's data in any form. So, we don't need any further consent to publish our article.

Availability of data and Materials: As reported at the end of the Method Section "Availability of data herein utilized can be found at the following links: www.moebius-italia.it and www.istat.it."

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Authors contribution: All the listed authors gave a significant contribution in preparing, analyzing and discussing the data reported in the present work and, according to the EMWA guidelines for scientific writers, each of them can be included as an "Author"

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Tables

Table 1. Relative rate (%) of MBS in the five Italian regions.

	No. of cases (N)	Age range at diagnosis (years)	No. of males (M)	% Males	No. of females (F)	% Females
Northeast	35	0–38	16	45.7	19	54.3
Northwest	51	0–55	19	37.3	32	62.7
Central	34	0–49	16	47.1	18	52.9
South	29	0–34	15	51.7	14	48.3
Islands	15	0–18	7	46.7	8	53.3
Total	164	0–55	73	44.5	91	55.5

Table 2. Prevalence (including gender-specific) of MBS in each region.

	P-TT Tot cases/Pop[a] (per 100,000)	P-MT M cases/Pop[a] (per 100,000)	P-FT F cases/Pop[a] (per 100,000)	P-MM M cases/M-Pop[b] (per 100,000)	P-FF F cases/F-Pop[c] (per 100,000)
Northeast	0.30	0.14	0.16	0.28	0.32
Northwest	0.32	0.12	0.20	0.24	0.39
Central	0.28	0.13	0.15	0.27	0.29
South	0.21	0.11	0.10	0.22	0.19
Islands	0.22	0.10	0.12	0.22	0.23
Total	0.27	0.12	0.15	0.25	0.29

Figures

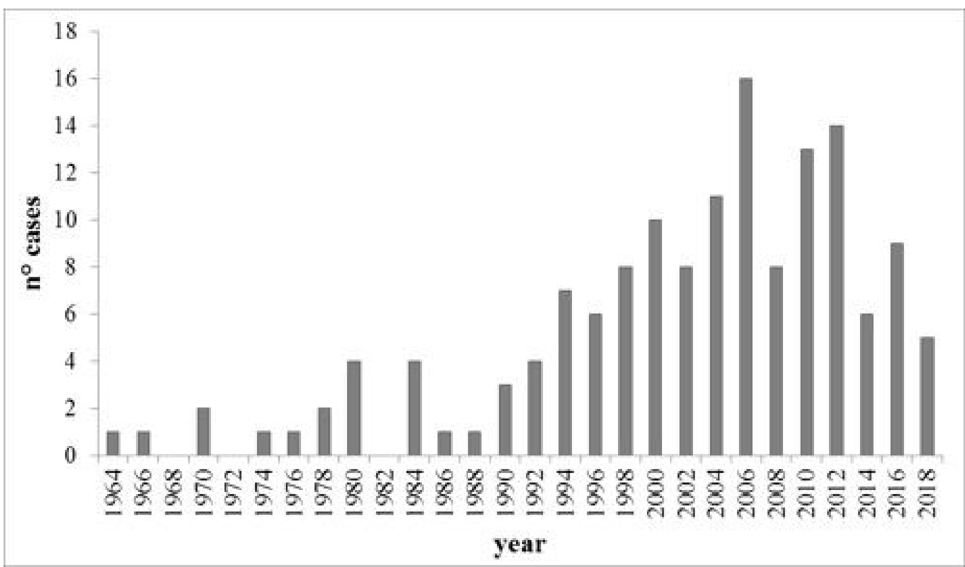
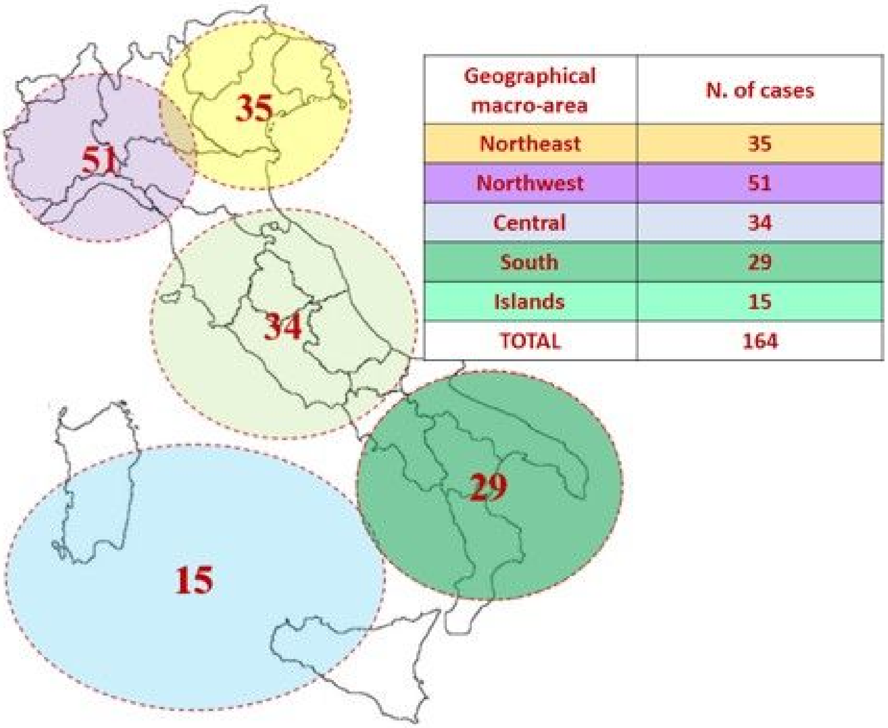


Figure 1

Number of newly recorded MBS cases in each biennium from 1964 to 2018. Cases registered in odd years were assigned to the next even year.



Geographical macro-area	N. of cases
Northeast	35
Northwest	51
Central	34
South	29
Islands	15
TOTAL	164

Figure 2

The prevalence of MBS (no. of cases/100,000 people) was determined for each geographic area (Table 2), with an overall prevalence of 0.27/100,000.