# Title

Will the real Moebius syndrome please stand up? A systematic review of the literature and statistical cluster analysis of clinical features.

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# Abstract

Moebius syndrome is a highly variable syndrome with abducens and facial nerve palsy as core features. Strict diagnostic criteria do not exist and the inconsistency of the associated features makes determination difficult. To determine what features are associated with Moebius syndrome we performed a systematic literature review resulting in a composite case series of 449 individuals labelled with Moebius syndrome. We applied minimum criteria (facial and abducens palsy) to determine the prevalence of associated clinical features in this series. Additionally, we performed statistical cluster analysis to determine which features tended to occur together. Our study comprises the largest series of patients with Moebius syndrome and the first to apply statistical methodology to elucidate clinical relationships. We present evidence for two groups within the Moebius diagnosis. Type 1: exhibiting micrognathia, limb anomalies and feeding / swallowing difficulty that tend to occur together. Type 2: phenotypically diverse but more associated with radiologically detectable neurologic abnormalities and developmental delay.

# Keywords

Moebius Syndrome; classification; statistics and numerical data; genetics; diagnostic imaging.

**Main text**

# Introduction

Described in 1880 by Graefe (Von Graefe & Saemisch, 1880) and then by its namesake in 1888, (Möbius, 1888) Moebius syndrome (MBS) came to describe a non-progressive bilateral facial and abducens palsy. Since then, despite the recognition of associations with various other features, further classification or even a clear definition of the syndrome has proven problematic.

*Current definitions*

The first attempts to further define MBS beyond these original descriptions included Richards, who adjusted the definition to include unilateral and/or partial facial or abducens palsies and requiring congenital limb abnormalities (Richards, 1953). Others considered any combination of sixth and seventh nerve deficits as MBS, with deformities of the extremities a common, but non-diagnostic feature (Verzijl, van der Zwaag, Cruysberg, & Padberg, 2003). More recently Kumar et al proposed facial nerve paralysis as the only essential feature for diagnosis, but isolated facial nerve paralysis is more properly classified as hereditary congenital facial palsy (HCFP) (Kumar, 1990; Verzijl, Padberg, & Zwarts, 2005; Verzijl et al., 2003). Based on ophthalmic findings, MacKinnon et al suggested that intact vertical gaze should be considered a minimum diagnostic criterion (Mackinnon et al., 2014). But in spite of these efforts, no consensus of the core clinical features described over 100 years ago has been agreed upon. A summary of definitions from commonly used sources is in table 1.

It is currently widely accepted that MBS is a rhombencephalic disorder with a heterogeneous etiology (Verzijl et al., 2005; Verzijl et al., 2003).

It has a highly variable presentation, generally regarded as *specifically* affecting abducens (VI) and facial (VII) nerve function with involvement of other cranial nerves as well as other cranial and extra-cranial dysmorphisms. Mendelian Inheritance in Man records the basic description as “congenital facial palsy with impairment of ocular abduction” (OMIM: 157900). This was further refined at the Moebius Syndrome Foundation Research Conference in 2007 as a “congenital, non-progressive facial weakness with limited abduction of one or both eyes” (Miller, 2007). These comprise the minimum diagnostic criteria (MDC) for this study.

The problem of definition is twofold: first that the condition is rare; such that studies of the frequencies of associated features are few (Carta, Mora, Neri, Favilla, & Sadun, 2011; Henderson, 1939; Mackinnon et al., 2014; Verzijl et al., 2003). Second, the wide variety of associated features of MBS introduces diagnostic confusion. Features of MBS overlap with other cranial dysinnervation disorders, Poland syndrome and myopathic disorders (Gutowski & Chilton, 2015).

Clarification of the definition of MBS is important as the rarity and variety of presentation makes diagnosis difficult. It may also allow the identification of distinct phenotypes and guide research towards a better understanding of etiology. The purpose of this study was to describe the prevalence of clinical features in MBS and to evaluate associations between these features.

# Methods

A review of the English language literature (1946 to 2016) was performed using PubMed and the NHS Evidence Databases (AMED, EMBASE, HMIC, MEDLINE, PsycINFO, British Nursing Index, CINHAL and Health Business Elite). Inclusion and exclusion criteria were agreed and formalized before data extraction and analysis (table 2). Citations retrieval and selection was performed by two authors independently (AYF and CB) before the reviewers established consensus; a clinical geneticists was involved in selection and review of articles (VMcK).

A broad search was performed using the terms [Moebius], [Mobius], [Möbius], [sequence], [anomaly], and [syndrome] to generate a list of 1010 titles. The titles and abstracts were evaluated using the inclusion and exclusion criteria for relevance. When there was doubt with regard to relevance, the full text article was to be retrieved. Before establishing consensus the kappa statistic was calculated to determine agreement for full-text article retrieval; κ= 0.992 suggesting excellent agreement.

Figure 1 outlines the article selection process. A total of 213 unique articles were retrieved for full text review. 94 were discounted: 24 did not meet MDC, 34 had insufficient phenotypic information, 5 had other major anomalies (e.g. holoprosencephaly, myotonic dystrophy or hypoxic brain injury), 11 were not in English (but had English abstracts), 12 were abstracts, letters or review articles that did not present clinical case reports, 7 were duplicated patients presented in other retrieved articles (the information was amalgamated based on the most recent report) and one article could not be obtained. This left 119 articles remaining for analysis.

The bibliographies of all the selected publications were reviewed to identify a further 25 reports that were not found in the database search using the same criteria. This yielded a total of 144 full text articles that comprised a total of 454 patients (references for these articles are included in the appendix). Clinical features were extracted from the texts and defined as “present”, “absent” or “not specified”. Free text entries were used to detail information from each report.

Multivariate analysis was used to identify whether certain clinical features tended to occur together. A complete linkage method of cluster analysis was used to determine which features were most related to each other. In order to provide the most informative results, patients with at least one of the 26 most commonly reported features (documented in at least 20% of patients) were selected for cluster analysis (n=395), representing 87% of the entire cohort. Dissimilarity was measured using Gower’s general similarity coefficient. As facial and abducens nerve palsy were recorded and present in 100% of patients, these features were excluded. Associations between features were analysed using a chi-squared test. In order to minimise type 1 error, features were only chosen for this analysis if they were thought to have a feasible statistical or clinical association to each other. This included those who had a close relationship in the cluster analysis, those that have been shown to be associated in previous studies, or those that have an anatomic or pathologic connection.

# Results

*Prevalence of Clinical features*

All patients exhibited both VII and VI palsy (as per our definition); facial palsy was bilateral in 82.4% of patients and abducens palsy was bilateral in 91.9% of patients. There was a slight male preponderance comprising 57.7% of patients (n=345). In order to exclude the known association between Poland anomaly and male sex, we recalculated this excluding those patients with Poland anomaly and found 48.6% of patients were male. Tables 3-5 present the clinical features described by the articles in this series of patients (full results of clinical features in supplementary table A). The most common features reported were dysarthria, swallowing difficulties and abnormal motor coordination (in older children) and hypotonia and failure to thrive (in younger children). Commonly reported physical features were micrognathia, epicanthic folds, mild ear anomalies and atrophic tongue; approximately 70% exhibited developmental delay. A crude analysis comparing the number of associated features with unilateral versus bilateral VII palsy suggested that there were more associated anomalies in those with bilateral palsies (P=0.001; *t*-test). Limited numbers of patients with unilateral palsy precluded further meaningful analysis.

Other cranial nerves were commonly affected, most frequently the vagus (53%), hypoglossal (45%) and oculomotor nerve (48%; table 3). Imaging abnormalities of the brain were identified in 66% of patients (n=63) typically calcifications, hypoplasia of the brainstem (pons, medulla or both), hypoplasia of the facial colliculus, abnormalities of the floor of the 4th ventricle, ventricular dilatation or callosal abnormalities (supplementary table B). Calcification in the CNS was present in 51% on pathologic or imaging examination. In a small number of reports, brainstem histopathology was presented demonstrating the abducens nucleus or nerve was absent or hypoplastic in 50% of patients (n=22) and the facial nerve or nucleus was similarly abnormal in 59% of patients (n=26).

A high-arched palate or overt cleft palate was present in 70.5%. Cardiac anomalies such as dextrocardia and septal defects occurred in 33%. Limb anomalies are summarised in table 3, with more than 50% exhibiting some form of upper or lower limb anomaly. The well-documented association with Poland anomaly was present in 38% of patients; this will be explored in greater detail in another paper. Scoliosis was present in 34%.

Genetic mutations were found in 12% of patients (see supplementary table C) the remainder reported no abnormality detected. Abnormalities during pregnancy included use of cocaine (6%; n=34), ergotamine (13%; n=38), misoprostol (28%; n=28), intrapartum bleeding (44%; n=45) but are likely to be subject to reporting bias. Similarly, features such as epilepsy (90%; n=10), hypogonadism (100%; n=4) and sleep disturbance (100%; n=3) were reported by papers in which this clinical feature was the primary subject. Notably, 10/454 patients required long term ventilation and 20/454 died of aspiration pneumonia or apnoea during infancy.

*Cluster analysis results.*

Cluster analysis groups objects (or features) together such that those in one group are more related to each other than those of another group. This technique is used in many fields including pattern recognition, bioinformatics and machine learning. In this instance, hierarchical clustering produces a dendrogram that visually represents the linkage between different features (Figure 2). In this paper we term clustering to mean the tendency for clinical features to occur together in the same individual. In our analysis, the cut off for interpreting the linkage is greater than 50% of the x-axis. Using this, two clusters of clinical features were identified. The first group exhibited limb abnormalities (including Poland syndrome), swallowing/feeding difficulties and micrognathia (Type 1: which we colloquially termed the ‘less severe’ group). The second included developmental delay, failure to thrive, additional cranial nerve palsies, palatal and brain imaging abnormalities (Type 2: a ‘more severe’ group).

Both clusters were further explored for degree of association: This was statistically significant for swallowing/feeding difficulties and micrognathia (p=0.065), micrognathia and limb abnormality (p=0.016), and swallowing difficulty and limb abnormality (p=0.027). These core features of the ‘less severe’ group tend to occur together (table 4). There was a significant association between Poland syndrome and male sex (p<0.001).

The patients in the ‘more severe’ cluster are more variable in terms of their clinical features but do not cluster as tightly together (table 5). In particular developmental delay has a strong association with failure to thrive (p<0.001). In spite of their shared neural crest etiology, an association between cleft palate and cardiac anomalies not found. Family history or genetic abnormality was not clearly associated with type 2 patients (p=0.082).

Cranial nerve abnormalities were tested for association due to their anatomic relationship. When systematically compared using chi-squared analysis, palsy in any included cranial nerve (III, IV, V, IX, X, XI XII) was generally significantly associated with any other (p<0.01) except for nerves III vs V, III vs XII and IV vs XII (table 6).

# Discussion

Confirmation of discrete clinical patterns in MBS could lead to an improved understanding of the etiology, but defining it has long proved difficult and relied on level IV evidence at best (Mackinnon et al., 2014; Verzijl et al., 2003). For other entities, an improved and agreed definition has proven beneficial. CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) was first reported as a collection of repeated clinical associations to choanal atresia, with an unknown etiology (Hall, 1979; Hittner, Hirsch, Kreh, & Rudolph, 1979). Further case series were published based on the recognition of these associations leading to the proposition of the CHARGE acronym and the first diagnostic criteria (Pagon, Graham, Zonana, & Yong, 1981). Attempts at improving the criteria have been several, from simply using larger case series (Tellier et al., 1998), to collecting case reports from various sources and applying a computer model (Mitchell, Davenport, Hefner, & Shei, 1985), or analysing a large pool of patients from congenital malformations registries (Harris, Robert, & Källén, 1997). Thus later attempts at refinement into more clinically relevant and useful criteria had a basis in larger empirical studies (Blake, Hartshorne, Lawand, Dailor, & Thelin, 2008; Verloes, 2005). Accurate diagnosis of CHARGE syndrome led to productive genetic discovery and testing; a specific genetic locus can now be identified in most cases of CHARGE syndrome (Hale, Niederriter, Green, & Martin, 2016; Lalani et al., 2006). Similar examples can be found in various other diseases, for example APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) or LEOPARD (multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness).

LEOPARD:

Gorlin, R. J., Anderson, R. C., Blaw, M. E. Multiple lentigines syndrome: complex comprising multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, sensorineural deafness, and autosomal dominant hereditary pattern. Am. J. Dis. Child. 117: 652-662, 1969. [PubMed: 5771505]

Voron, D. A., Hatfield, H. H., Kalkhoff, R. K. Multiple lentigines syndrome: case report and review of the literature. Am. J. Med. 60: 447-456, 1976.

Coppin, B. D., Temple, I. K. Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis). J. Med. Genet. 34: 582-586, 1997. [PubMed: 9222968, related citations] [Full Text]

Digilio, M. C., Sarkozy, A., de Zorzi, A., Pacileo, G., Limongelli, G., Mingarelli, R., Calabro, R., Marino, B., Dallapiccola, B. LEOPARD syndrome: clinical diagnosis in the first year of life. Am. J. Med. Genet. 140A: 740-746, 2006. [PubMed: 16523510, related citations] [Full Text]

LEOPARD Syndrome: Clinical Aspects and Molecular Pathogenesis

Sarkozy A.a · Digilio M.C.b · Zampino G.c · Dallapiccola B.a · Tartaglia M.d · Gelb B.D.e In: Zenker M (ed) (ed): Noonan Syndrome and Related Disorders - A Matter of Deregulated Ras Signaling. Monogr Hum Genet. Basel, Karger, 2009, vol 17, pp 55-65

<https://doi.org/10.1159/000164839>

APECED:

Neufeld, M., Maclaren, N. K., Blizzard, R. M. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. Medicine 60: 355-362, 1981. [PubMed: 7024719]

Betterle, C., Greggio, N. A., Volpato, M. Autoimmune polyglandular syndrome type 1. J. Clin. Endocr. Metab. 83: 1049-1055, 1998. [PubMed: [9543115](https://www.ncbi.nlm.nih.gov/pubmed/9543115)] [[Full Text](https://academic.oup.com/jcem/article-lookup/doi/10.1210/jcem.83.4.4682)]

Beyond APECED: An update on the role of the autoimmune regulator gene (AIRE) in physiology and disease. Conteduca, Giuseppina. Autoimmunity reviews Volume: 17 Issue 4 (2018) ISSN: 1568-9972 Online ISSN: 1873-0183

*Methodology*

Such achievements have proven more difficult for MBS. Until recently, the vast majority of studies have involved case reports or small series. Some slightly larger studies have focussed on one particular aspect, such as speech and language acquisition (Meyerson & Foushee, 1978), or autism spectrum disorder (Briegel, Schimek, Kamp-Becker, Hofmann, & Schwab, 2009). Verzjil’s 2003 study of 37 patients was the largest at the time and provided detailed information on all clinical features of the patients (Verzijl et al., 2003). This has formed the basis of our current understanding of the frequency of these features (e.g. OMIM uses it). However, there has been an accumulation of case reports and series in the literature; our analysis is the first to apply systematic review methodology to this repository of data to ascertain the phenotypic profile of MBS. Although the kappa statistic for full-text article retrieval indicated excellent agreement, this may be due to the necessarily broad criteria. The exclusion of non-English articles does not bias the analysis generally (Moher et al., 2000), but may for specific areas where cultural issues are relevant, such as the use of the abortifacient misoprostol in South America.

The nature of secondary analysis means reporting biases are inevitable – specifically manifest as under-reporting ‘important negatives’. Case reports tended to note features present rather than those absent, reducing the quality and consistency of the total information gathered. In order to minimise this, our cluster analysis used only features that were documented as ‘present’ or ‘absent’ and ignored studies in which absence of a feature was not documented.

Our reliance on the literature removes the consistency of clinical examination by professionals experienced with the condition. For example, esotropia or strabismus can be confused with failure of abduction. In one study by experienced clinicians, 18% of patients with a ‘diagnosis’ of MBS had full eye abduction, and were subsequently re-diagnosed with other conditions such as HCFP or congenital fibrosis of the extraocular muscles (CFEOM) type 3A (Mackinnon et al., 2014). In our own study, one patient had a *KIF21A* mutation consistent with CFEOM and 7 patients had an ‘additional’ diagnosis of CFEOM. Thus the use of the Moebius Syndrome Foundation criteria (Miller, 2007) in our methodology meant that some syndromes we would not consider MBS were included (as ‘reported MBS’): they are sensitive but not specific. As such we support the assertion that intact vertical gaze be adopted as a diagnostic criterion. We believe that this will help to exclude the majority of genetically distinct diagnoses such as HCFP or CFEOM, and prompt further investigation in the clinical setting. Despite these weaknesses, this study remains the single largest composite series compiled in the literature.

*Prevalence data*

In this study we have examined the prevalence of clinical findings associated with a diagnosis of MBS with VI and VII nerve palsy. A slight male preponderance has never been commented upon previously, demonstrating the utility of examining larger case series. The prevalence of some features reported in the Verzjil study are broadly reflected in our data, but the two studies are not directly comparable due to reporting bias and different diagnostic criteria between studies. Similarly, those features described as 100% prevalent in small case series (e.g. hypogonadism, sleep disturbance) were regarded due to reporting bias and their true prevalence remains to be determined. Anecdotally, sleep disturbance is a commonly reported feature but no large case series examines this.

A constellation of oro-motor clinical signs such as micrognathia, swallowing difficulty, small (atrophic) tongue and hypoglossal nerve palsy were very common; cleft palate was present in 38% of patients. These likely account for the high prevalence of failure to thrive (FTT) and dysarthria but this study cannot confirm causation. Micrognathia and swallowing difficulty are subjective signs without clear diagnostic criteria and are difficult to quantify. However, both dysarthria and FTT are objective determinants and should prompt further examination for additional features.

Limb anomalies were present in 75% of patients with the prevalence of lower limb anomalies being 62%. Talipes was present in over 50% of patients, more common than Poland anomaly which was present in 38% of patients. We confirm the previously documented association between male sex and Poland syndrome in the context of MBS (Parker, Mitchell, & Holmes, 1981; Verzijl et al., 2003). We will explore the relationship between MBS and Poland syndrome further in a separate study.

Hypotonia in younger children and abnormal motor coordination were present in 80-90% of patients. This poor coordination is generally greater than one would expect from any associated physical disability and may indicate generalised neuronal dysgenesis. *PLXND1* is a member of the plexin family of transmembrane receptors involved in axon guidance and cell-cell contact. Although previously excluded as a cause of MBS (van der Zwaag et al., 2004), it has been shown to be mutated in MBS and is probably a rare cause (Tomas-Roca et al., 2015). This suggests that the disorder may encompass neural connection issues in addition to anatomically detectable abnormalities of cranial nerve nuclei.

*Cluster analysis*

Patterns within the MBS spectrum have been recognised and proposed. Verzijl et al showed that in a majority of their patients there was a co-occurrence of bilateral facial nerve and eye abduction impairment, hypoglossia, craniofacial and limb malformations, and long tract symptoms (Verzijl et al., 2003) and suggest this could represent a distinct phenotype. They found no association found within these broad categories of clinical features; but their analysis is limited by the number of patients. This study has gone one step further and is the first to examine the majority of published case reports and apply statistical methodology to search for associations. We found strong clustering of micrognathia, limb deformities, and feeding / swallowing difficulties. This suggests a specific pattern in a number of patients with these findings (63% of patients with *any* of these features had *all* of these features; table 4). This is the first time this relationship has been reported.

By contrast, clustering in the more severe group was present but weaker (table 5). Family history or genetic abnormality was not clearly associated with Type 2 patients. This is likely due to the low numbers of patients with such data recorded and a large number of studies conducted before sophisticated genetic testing was widely available. Reappraisal of the prevalence and clustering of the clinical features will allow clinicians to target their examination and investigations more precisely. Imaging and pathologic presence of brain abnormality was common (66%; supplementary table A) and we now perform a MRI scan on all patients to support diagnosis or look for associated anomalies. A further paper is currently in preparation to more fully discuss the practical recommendations that result from this analysis.

*Genetics*

Although most cases of MBS have been considered sporadic, that MBS can be heritable has been appreciated for decades (Becker-Christensen & Lund, 1974; Legum, Godel, & Nemet, 1981; Stabile et al., 1984; Wishnick, Nelsona, Huppert, & Reich, 1983). Although progress has been made in the understanding of the genetics of MBS, no single gene locus has been identified in a large number of patients. The majority of case reports in the literature did not have the benefit of modern sequencing technology. As a result, we do not believe that we can use these reports to evaluate the frequency of genetic mutations with any accuracy. However, the wide spectrum of the MBS phenotype does not rule out a unifying cause: genes do not code for anatomic structures, and disrupting different developmental processes can lead to a single common outcome (Fattah, 2017; Verzijl et al., 2003). For example, *MYMK* mutation leads to disruption of muscle formation (failure of myoblast fusion) and has been shown to result in Carey-Fineman-Ziter Syndrome (Di Gioia et al., 2017) and *STAC3* underlies Native American Myopathy (Telegrafi et al., 2017). Whereas genes coding for microtubule function (eg. *TUBB3, KIF21A*) result in dysinnervation of the extraocular muscles resulting in CFEOM or a hereditary non-progressive facial palsy (*TUBB6*; Fazeli et al., 2017). All of these have features overlapping with MBS and if found have important implication for genetic counselling as they have autosomal recessive (Carey-Fineman-Ziter Syndrome and Native American Myopathy) or autosomal dominant (CFEOM caused by *TUBB3* or *KIF21A* mutations and hereditary non-progressive facial palsy caused by *TUBB6* mutation) inheritance. Therefore they should be excluded prior to a diagnosis of “Moebius syndrome” being made.

*Etiology*

We provide statistical evidence for a strong association of multiple cranial nerve palsies, a relationship that has been anecdotally recognised previously (Henderson, 1939; Sudarshan & Goldie, 1985). Given the anatomic proximity of the nuclei this supports the argument for a generalized midbrain-hindbrain etiology, at least in some patients (Barkovich, 2012; Towfighi, Marks, Palmer, & Vannucci, 1979; Verzijl et al., 2003). A complex patterning disorder of the brainstem still remains a more likely etiology rather than simple absence or hypoplasia of the cranial nerves (Towfighi et al., 1979; Verzijl et al., 2003).

*Difficulties in defining Moebius syndrome*

In this study we have examined the prevalence of clinical features associated with patients that have a VII and VI palsy and have been labelled with the diagnosis of MBS. In addition, we have used statistical methods to determine whether specific features tend to occur together. One of the most difficult barriers to agreed definitions of the syndrome is the fact that many of the clinical features (e.g. micrognathia, hypotonia) lack objective definitions. Even if a list of agreed features could be compiled then subjective decisions on whether such features are present or not may still hamper diagnosis. From this study, clinical features associated with facial and abducens palsy are not consistent enough to present clear-cut diagnostic criteria. Subsequent reports and other empirical studies should comment on the absence or presence of the features presented in this study to improve reporting and allow for more accurate analyses in future. We welcome collaboration to agree diagnostic criteria for MBS.

**Conclusion**

Our study comprises the largest composite series of MBS cases and the first to apply statistical methodology to elucidate clinical relationships in patients diagnosed with MBS and confirmed VI and VII palsy. As a result we present evidence for two groups: type 1: with a strong association between micrognathia, limb anomalies, and feeding difficulties; and type 2: a more diverse group with learning disabilities, failure to thrive, cranial nerve deficits, and an identifiable brain abnormality. We hope this may be used as the basis for a Delphi consensus to allow for an international collaborative effort towards criteria that can be widely adopted.

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# Conflict of interest statement

The authors have no conflicts of interest to declare.

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# Tables

Table 1: Current definitions of Moebius syndrome.

|  |  |  |  |
| --- | --- | --- | --- |
| **Source** | **Facial palsy** | **Impaired eye abduction** | **Other features** |
| OMIM† | Yes | Yes | None required for diagnosis |
| Gorlin‡ | Yes | Yes | None required for diagnosis |
| Orphanet§ | Yes; complete or incomplete | Yes; bilateral | None required for diagnosis |

Features are congenital and non-progressive. †OMIM: 157900; ‡(Hennekam, Krantz, & Allanson, 2010); §ORPHA:570.

Table 2: Inclusion and exclusion criteria for title and abstract retrieval.

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| Case report | Overlapping case series |
| Case series | No / non-clinical data |
| Clinical features documented | Inadequate information |
| Cranial nerves VI and VII affected | Not English |

Table 3: Features of Moebius syndrome associated with the minimum diagnostic criteria.

|  |  |  |  |
| --- | --- | --- | --- |
| **Feature** | **Cases where feature recorded** | **Total cases positive for feature** | **Percentage of recorded cases positive for feature** |
| **General features** |
| Dysarthria | 74 | 66 | 89.2% |
| Abnormal motor coordination | 62 | 53 | 85.5% |
| Failure to thrive | 177 | 140 | 79.1% |
| Micrognathia | 139 | 105 | 75.5% |
| Hypotonia | 69 | 52 | 75.4% |
| Epicanthic folds | 123 | 90 | 73.2% |
| Developmental delay | 182 | 128 | 70.3% |
| Swallowing difficulties\*older | 122 | 82 | 67.2% |
| Brain imaging abnormality | 96 | 63 | 65.6% |
| Ears dysplastic or low set | 81 | 53 | 65.4% |
| Hypoplastic tongue | 189 | 119 | 63.0% |
| High palatal arch | 81 | 50 | 61.7% |
| Blepharoptosis | 71 | 29 | 40.8% |
| Cleft palate | 114 | 43 | 37.7% |
| Cardiac anomalies | 69 | 23 | 33.3% |
| Conductive deafness | 61 | 15 | 24.6% |
|  **Cranial nerve palsies** |
| CN I | 1 | 1 | - |
| CN II | - | - | - |
| CN III | 93 | 45 | 48.4% |
| CN IV | 64 | 24 | 37.5% |
| CN V | 121 | 31 | 25.6% |
| CN VIII | 91 | 28 | 30.8% |
| CN IX | 71 | 31 | 43.7% |
| CN X | 83 | 44 | 53.0% |
| CN XI | 46 | 10 | 21.7% |
| CN XII | 159 | 72 | 45.3% |
| **Limb and skeletal anomalies** |
| Any lower limb anomaly | 210 | 131 | 62.4% |
| Any upper limb anomaly | 252 | 137 | 55.4% |
| Talipes | 185 | 98 | 53.0% |
| Brachydactyly | 95 | 45 | 47.4% |
| Poland anomaly | 170 | 65 | 38.2% |
| Syndactyly | 111 | 40 | 36.0% |
| Scoliosis  | 70 | 24 | 34.3% |
| Symbrachydactyly | 78 | 16 | 20.5% |
| Camptodactyly | 59 | 10 | 16.9% |

CN = cranial nerve

Table 4: Association of features in patients with ‘type 1’ Moebius syndrome.

|  |  |
| --- | --- |
|  | **Any limb abnormality** |
| No | Yes |
| **Feeding or swallowing difficulty** | **Feeding or swallowing difficulty** |
| No | Yes | No | Yes |
| **Total** |
| **Micrognathia** | No | 2 | 4 | 3 | 8 | **17 (21%)** |
| Yes | 2 | 5 | 6 | 52† | **65 (79%)** |
| **Total** | **4 (5%)** | **9 (11%)** | **9 (11%)** | **60 (73%)** | **82** |

†Patients with all three features represent 63% of those with any of these features.

Table 5: Association of features in patients with ‘type 2’ Moebius syndrome (cranial nerves are not included due to the heterogeneity of the data).

|  |  |
| --- | --- |
|  | **Failure to thrive or feeding / swallowing difficulties**  |
| No | Yes |
| **Brain abnormality on imaging or at autopsy** | **Brain abnormality on imaging or at autopsy** |
| No | Yes | No | Yes |
| **Total** |
| **Developmental delay** | No | 0 | 2 | 1 | 2 | **5 (13%)** |
| Yes | 0 | 2 | 8 | 24† | **34 (87%)** |
| **Total** | **0** | **4 (10%)** | **9 (23%)** | **26 (67%)** | **39** |

†Patients with all three features represent 62% of those with any of these features.

Table 6: Statistical association between involvement of the various cranial nerve in Moebius syndrome.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CN III** | **CN IV** | **CN V** | **CN IX** | **CN X** | **CN XI** | **CN XII** |
| **CN III** |   | <0.001 | 0.071 | 0.007 | 0.008 | 0.003 | 0.055 |
| **CN IV** | <0.001 |   | 0.004 | 0.006 | 0.002 | 0.003 | 0.227 |
| **CN V** | 0.071 | 0.004 |   | <0.001 | <0.001 | 0.004 | <0.001 |
| **CN IX** | 0.007 | 0.006 | <0.001 |   | <0.001 | 0.004 | <0.001 |
| **CN X** | 0.008 | 0.002 | <0.001 | <0.001 |   | <0.001 | <0.001 |
| **CN XI** | 0.003 | 0.003 | 0.004 | 0.004 | <0.001 |   | 0.001 |
| **CN XII** | 0.055 | 0.227 | <0.001 | <0.001 | <0.001 | 0.001 |   |

CN = cranial nerve. All values are p values.

# Figure legends

Figure 1: \*Did not meet minimum diagnostic criteria n = 24; insufficient phenotypic information n = 34; had other major anomalies n =5; not in English n = 11; abstracts, letters or review articles not presenting clinical cases n = 12; duplicated cases presented in other included articles n = 7; could not be obtained n = 1.

Figure 2: NOS = not otherwise specified; FTT = failure to thrive.