Möbius Syndrome

Janakie Singham, B.Sc.,[1] Ralph Manktelow, M.D., F.R.C.S.(C),[2] and Ronald M. Zuker, M.D., F.R.C.S.(C)[3]

ABSTRACT

Möbius syndrome is classically defined as combined congenital bilateral facial and abducens nerve palsies, although it may also be associated with a myriad of other craniofacial, musculoskeletal, cardiothoracic, endocrinologic, and developmental disorders. The problem that most patients complain about, however, is the inability to smile and close their lips while eating. Although the etiology of this syndrome is still unknown, scientific support has been growing for the hypothesis that it is due to an embryological disruption of subclavian artery development. The treatment of choice for facial reanimation in these patients is a neurovascular free muscle transfer, ideally using the gracilis muscle with direct repair of the gracilis muscle's motor nerve to the masseteric branch of the trigeminal nerve. If the masseteric nerve is unavailable, a partial hypoglossal or accessory nerve may be used. These operations, enhanced by the effects of cerebral plasticity, may allow Möbius patients to reach their goals of satisfactory spontaneous smiles.

KEYWORDS: Möbius syndrome, facial paralysis, facial diplegia, facial reanimation, gracilis flap transfer

Möbius syndrome is a constellation of congenital malformations and clinical dysfunctions that spans the domains of many different medical specialties. It was first described as a curious combination of horizontal gaze palsy and bilateral facial paralysis by von Graefe in his Handbook of Ophthalmology in 1880.[1] German neurologist Paul Möbius subsequently published a landmark article comparing his own cases of combined abducens and facial nerve palsies with other published case reports in 1888, thus officially giving birth to the syndrome that now bears his name.[2,3] Continued clinical observations led to the realization that such combined cranial nerve VI and VII palsies were also associated with various craniofacial, cardiothoracic, endocrinologic, and developmental disorders, therefore necessitating the involvement of plastic surgeons, ophthalmologists, oral surgeons, otolaryngologists, cardiac surgeons, and those in many other medical disciplines. As its mysterious etiology confounds geneticists, pathologists, and epidemiologists alike, Möbius syndrome is truly a clinical entity of panmedical interest and importance.

DEFINITION AND CLINICAL FEATURES

As Möbius syndrome may have a myriad of associated clinical features, with consistency prevailing only in the presence of facial and abducens nerve palsy, Möbius syndrome is classically described as combined congenital bilateral abducens and facial nerve palsies. Subsequent studies have recognized that there may also be involvement of other cranial nerves. In order of decreasing frequency, these nerves are XII, X, IX, III VIII, V, IV, and XI.[4] The clinical findings associated with the bilateral facial nerve palsy during infancy include incomplete eye closure during sleep, drooling, and difficulty sucking.[5–8] With ensuing development, a classic emotionless

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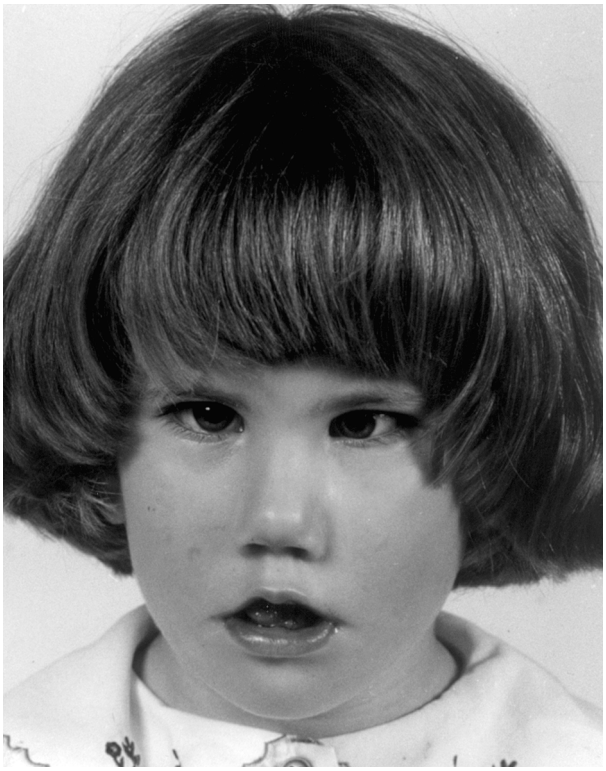

Figure 1 Preoperative view, at rest.

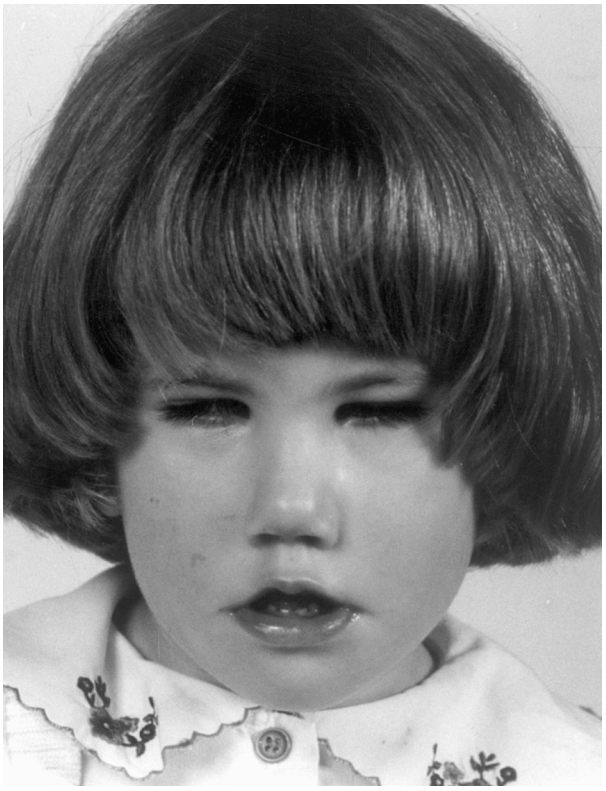

Figure 2 Preoperative view, maximal expression.

"mask-like facies" is noticed, with an inability to produce a facial expression or smile (Figs. 1, 2). Epiphora and ectropion due to lagophthalmos and eversion of the lacrimal puncta are also common in adult life.[7–9] The inability to close and thus protect the eye may result in recurrent or chronic conjunctivitis, although this is not usually evident until later in life. The abducens nerve paralysis is manifest as a horizontal gaze palsy, which is usually bilateral.[10–12] As cranial nerves III and IV are rarely involved, patients may also present with limited adduction or vertical gaze palsies.[10–12] Esotropia, however, is the most commonly found form of strabismus.[10–12]

Many musculoskeletal malformations are also occasionally associated with Möbius syndrome. Although clubfeet are the most commonly associated anomaly, brachydactyly, syndactyly, ectrodactyly, acheiria, arthrogryposis, kyphosis, kypholordosis, absent or rudimentary fingers or toes, and rib defects can also be found in Möbius patients.[5,6,11,13–18] Möbius syndrome may also be associated with Poland's anomaly, which is defined as congenital absence of the pectoral head with ipsilateral hand deformity.[14,16,19,20–22] Klippel-Feil anomaly (fusion of the cervical vertebrae into a single short bone), Goldenhar anomaly (absent serratus anterior muscle), and hypoglossia-hypodactyly may also be detected.[5,6,14,19,23,24] Associated myopathy and neuropathy have also been described.[15,25–28] The combination of Möbius syndrome, Robin sequence, and myopathy has been discovered in three individuals and has been named the Carey-Fineman-Ziter syndrome.[26] Endocrinological disorders such as Kallmann's syndrome (hypogonadotropic hypogonadism and anosmia) and premature thelarche have also been described in conjunction with Möbius.[26–29] Dextrocardia, ventricular septal defects, and transposition of the great vessels have been reported.[14,18,21,23] Common orofacial malformations include high arched (gothic) palate, cleft palate, fissured tongue, bifid uvula, micrognathia, retrognathia, hypodontia, malocclusion, microglossia, microstomia, dental caries, and periodontal disease.[30–32] Ocular problems such as keratoconus and compound hypertrophic astigmatism were also found.[12,33] Sleep disordered breathing, which is suspected to be due to lesions of the central respiratory neurons in the brainstem, may also be present.[34–36]

The reported incidence of mental retardation has varied from 10 to 75% in different studies.[5,6,12,37] Confounding features such as the blank expressionless face, poor articulation due to orofacial and glossal paralysis as well as velopharyngeal incompetence, and social introversion because of the inability to express emotion may all contribute to the false assumption of intellectual incapacity.[30,38–40] Contributing to the delay in speech development is the hearing loss commonly found in Möbius patients, which may be due either to cochlear nerve palsy or recurrent otitis media related to cleft palate anomalies.[41,42] Möbius syndrome has also been

associated with a high prevalence of autism, cerebral palsy, and childhood psychosis.[43–45]

DIAGNOSIS

As the definition of Möbius syndrome varies, so do its diagnostic criteria. Most clinicians diagnose Möbius syndrome in the presence of cranial nerve VII and VI palsies that can be either partial or complete and bilateral or unilateral. If partial, the lower components of the facial musculature, such as the depressor anguli oris, are usually functional. Kumar suggested the criteria for diagnosis in 1990 as (1) complete or partial facial nerve paralysis, which is essential for diagnosis; (2) limb malformations, which are often present; and (3) additional clinical features (as described earlier) that may be present.[6] The differential diagnosis for facial nerve palsy in infants includes facial nerve trauma during birth and supranuclear lesions.[46] Prenatal sonography, which may show decreased respiratory and swallowing movements, polyhydramnios, and related anomalies, may first alert the physician to the possible diagnosis of Möbius syndrome.[47,48] The differential diagnosis for Möbius syndrome includes other syndromes that combine cranial nerve palsies with craniofacial and limb abnormalities such as Hanhart syndrome, hypoglossia-hypodactyly syndrome, glossopalatine ankylosis, fascioscapulohumeral dystrophy, and Charlie M syndrome.[43,49–51]

ETIOLOGY

The clinical complexity of Möbius with its confusing array of malformations continues to hinder scientists in their pursuit to discover its etiology. Many syndromists believe that it is in fact not a syndrome at all but a sequence of anomalies that can be produced by a multitude of insults during a specific embryological period. The three traditional theories about the pathogenesis are (1) primary brainstem nuclear hypoplasia, (2) secondary brainstem nuclear degeneration, and (3) brainstem atrophy secondary to peripheral neuromuscular defects.[8,9,52–55] Scientific support has been growing, however, for the hypothesis suggested by Bouwes-Bavinck and Weaver in 1986 that Möbius syndrome is due to an embryological disruption of subclavian artery development.[23] The brainstem is originally supplied by the primitive trigeminal arteries (branches of the carotid), which then regress as the vertebral arteries start supplying the brainstem through the basilar artery. Premature regression, obstruction, and disruption of the primitive trigeminal arteries before full maturation of the brainstem's vascular supply are possible mechanisms by which multiple cranial nerve nuclei may become ischemic and dysfunctional.[23] Alternatively, obstruction or disruption of the vertebral or basilar artery can lead to similar brainstem ischemia and necrosis.[23] Pathological findings from autopsies show necrosis and calcification of the brainstem and cranial nerve nuclei, as would be seen after embryological ischemia to that region.[16,41,56–61] Radiological imaging, including ultrasonography, computed tomography, and magnetic resonance imaging, also shows such calcification and hypoplasia of the brainstem.[56,61–64] Many prenatal exposures and clinical events could possibly cause such a vascular disruption, including thalidomide, misoprostol, cocaine, benzodiazepines, ergotamine, alcohol, hypoxia, hypothermia, previous surgery, and failed abortion.[65–71] Studies have shown a strong correlation between prenatal misoprostol use and Möbius syndrome.[65–73] Many of the organs that follow an anomalous embryological course in Möbius syndrome, including the cranial nerve nuclei, the hand, the forearm, and the heart, develop between the fourth and sixth weeks.[22,24,58,68,74] Therefore, this is the proposed time period during which the insult is likely to occur.[8,23,24]

Although most cases of Möbius syndrome are sporadic, some familial trends have been seen with both autosomal dominant and recessive patterns.[8,71,75,76] The variable transmission pattern of familial Möbius syndrome suggests genetic heterogeneity and pleiotropism.[75,77] Various studies have suggested genetic causes related to 1;11 translocations, 1;13 translocations, 1;2 translocations, and microdeletion of band q12.2 on chromosome 13[78–81] Genes for Möbius syndrome have been localized to chromosome 10q and 3q, and cytogenetic characterization has shown a complex 46,XY,t(7;8;11;13) chromosomal rearrangement in a patient with Möbius syndrome.[82–84] The *SOX 14* gene on chromosome 3, which has been shown to play a role in limb bud outgrowth, may be involved in the etiology of Möbius syndrome.[85] Familial Möbius syndromes generally arise as cranial nerve palsies without musculoskeletal anomalies, and limb deformities rarely occur when the only paralyzed nerves are VI and VII.[4,42] When associated with musculoskeletal anomalies, Möbius syndrome is not likely to be familial, and thus the risk of genetic transmission to offspring is as low as 2%.[42] This transmission risk increases to 25 to 30% with clinical features that suggest a genetic etiology, such as the absence of skeletal defects, isolated facial palsy, deafness, ophthalmoplegia, and digital contractures.[42]

CLASSIFICATION

Möbius syndrome is a complex congenital anomaly and as such is hard to classify. Various attempts have been made and are of academic interest but to the practitioner are of little practical value.[43,51,86–88] However, it is helpful to identify the cranial nerves involved, the affected limbs, and any other associated deformities.[89,90] With respect to the involvement of cranial nerve VII, it is of practical value in the management of these patients to outline the

extent of bilateral involvement, the specific muscle groups affected, and any abnormal muscle groups that may produce unusual movements. In this way, the deformity can be analyzed and a treatment plan formulated.

TREATMENT

Although strabismus and cardiac surgery could often satisfactorily treat the other major dysfunctions associated with Möbius syndrome, facial reanimation has remained a challenge for many years.[91] The facial diplegia associated with the syndrome not only causes functional problems such as drooling, dysphagia, poor dental hygiene, and impaired bilabial speech but also produces an emotionless face that can be socially stifling. The most common goals expressed by Möbius patients are to be able to smile and close the lips while eating. Timing of the surgery is usually after the age of 5, such that the vessels and nerves of the face have grown large enough to support a reliable muscle transfer. For bilateral facial involvement, one side of the face is done at a time with a minimum period of 3 months for recovery before the other side is operated on.

Although various static slings and local dynamic supports have been attempted, it was not until the emergence of microsurgery that Möbius patients had the prospect of a satisfactory smile. Static sling operations involve fascial strips from tensor fascia latae or lengths of tendon that are cut and shaped to support the oral commissure to the body of the zygoma and temporal fascia. The fascia is placed with sufficient tension to match the contralateral side symmetrically. As Möbius syndrome is often bilateral and this operation does not provide the dynamic reanimation most patients seek, it is no longer used in this population of patients. Local temporalis or masseter muscle transfers were initially used for reanimation, although these muscles may also be affected by Möbius syndrome and even if intact provide inadequate excursion to produce a full smile.[92–94]

The treatment of choice is a neurovascular free muscle transfer.[93,95–98] The most commonly used muscles are the gracilis and pectoralis minor. The gracilis muscle is particularly ideal as it is easily accessible, has a redundant purpose such that its harvest leaves no functional deficit, and has a reliable neurovascular pedicle. Terzis and Noah advocate the use of nerve grafts to utilize the rarely affected accessory nerve or the contralateral facial nerve even if only minimally functional.[89,90] A nerve graft may be necessary if the accessory nerve is to be used because of its position distal to the flap's neurovascular pedicle. Direct repair of the gracilis motor nerve to the motor nerve of the masseter is the senior author's procedure of choice. This nerve is usually available in patients with Möbius syndrome, is in the correct position for direct neurorrhaphy, provides very strong innervation to the muscle transfer, and provides

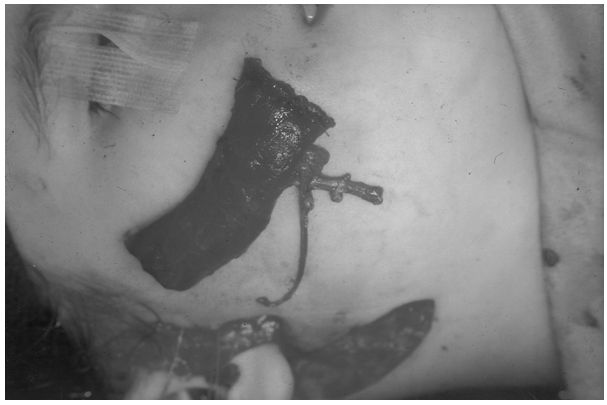

Figure 3 Intraoperative view, muscle in position.

innervation that can be easily controlled by the patient and often results in spontaneous smiling because of cerebral plasticity. If the masseteric motor branch is unavailable, partial hypoglossal or accessory nerve may be used.

During the gracilis muscle transfer, two teams of surgeons operate simultaneously to elevate the muscle and prepare the face. The gracilis muscle, which is based on the medial circumflex femoral artery or the profunda femoris artery, is dissected out and a longitudinal strip of muscle is transferred to the face. Usually ~50 to 60% of the gracilis circumference is utilized with sufficient length to traverse the distance between the oral commissure and the temporal fascia. The muscle is revascularized by microvascular repair of the gracilis muscle's artery to the facial artery and of the comitant veins of the gracilis to the facial vein. The motor nerve of the gracilis is coapted to the motor nerve to the masseter—the masseteric nerve. The distal end of the muscle is sutured securely to the oral commissure and the upper lip, and the origin is sutured with slight tension to the temporal and preauricular fascias (Fig. 3). With time, the masseteric nerve reinnervates the gracilis muscle transfer to reanimate the face (Figs. 4 and 5).

In addition to restoration of facial animation, in adult life Möbius patients may require surgeries that can help them close their eyes and thus protect their corneas from conjunctivitis and ulceration. Static support of the lower eyelid can be supplied by a tendon sling that is placed subcutaneously from the medial canthus to the lateral orbital margin. Dynamic eye closure can also be accomplished by the subcutaneous placement of 24 karat gold weights in the upper eyelid or by temporalis muscle transfer. More detailed descriptions of all the surgeries can be found in the senior author's book *Microvascular Reconstruction*.[99]

CONCLUSION

The complexity that makes Möbius syndrome one of the most challenging disorders also makes it one of

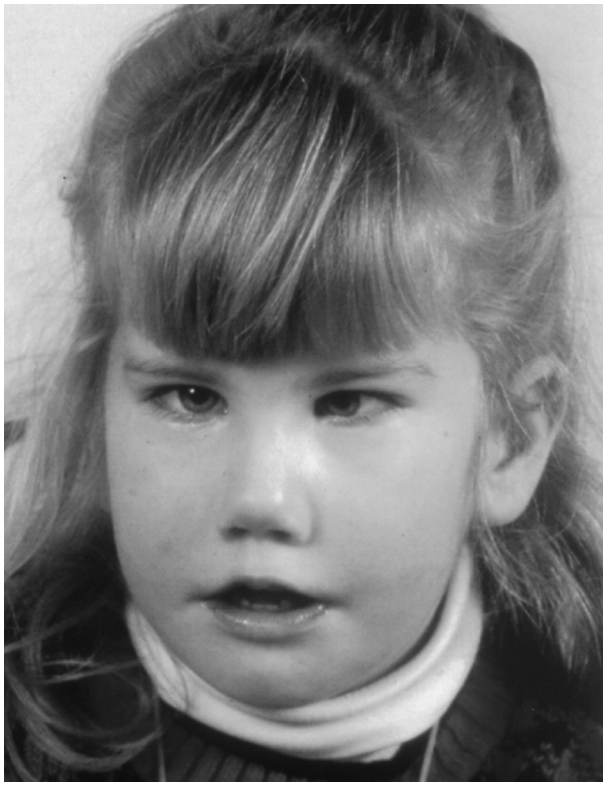

Figure 4 Postoperative view, at rest.

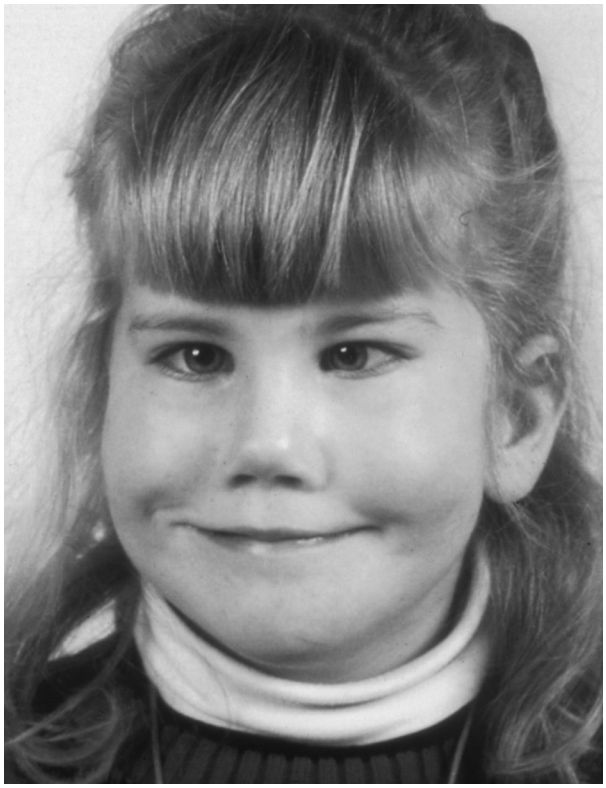

Figure 5 Postoperative view, with smile.

the most interesting. As clinicians strive to innovate new treatment, scientists aspire to explain its baffling amalgamation of anomalies. Research and progressive modifications of current surgical strategies continue, therefore, to achieve the ultimate clinical goal in this matter: a smile for the Möbius patient.

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