Child Neurology Open
Volume 10: 1-12

DOI: 10.1177/2329048X231205405
journals.sagepub.com/home/cno

Moebius Syndrome: An Updated Review of Literature

Syed Abdullah Monawwer, MBBS[1], Sajjad Ali, MBBS[1], Raahim Naeem, MBBS[2], Syed Hasan Ali, MBBS[2], Azkah Rabbani, MBBS[2], Maria Khan, MBBS[1], Saba Saleem Qazi, MBBS[1], Syed Muhammad Ismail Shah, MBBS[1], and Sabeeh Khawar Farooqui, MBBS[1]

Abstract

Moebius Syndrome, is a rare, non-progressive congenital neuropathological syndrome characterized primarily by the underdevelopment of the facial (CN VII) and abducens nerve (CN VI). Other features of Moebius Syndrome include facial nerve paresis, ophthalmoplegias, orthodontic deficiencies (including crowded dentition, swollen and hyperplastic gingiva, dental calculus, etc.), musculoskeletal abnormalities, and impaired mental function. Due to the rarity of the disorder, very few case studies have been reported in the literature. This article summarizes the significant features of the disease according to commonalities in reported cases, along with several newly recognized features cited in recent literature. We have explored the different diagnostic criteria and the newly recognized imaging modalities that may be used. Understandably, the condition detrimentally affects a patient's quality of life; thus, treatment measures have also been outlined. This study aims to provide updated literature on Moebius Syndrome MBS and improve understanding of the condition.

Keywords

Moebius syndrome, Poland syndrome, Facial nerve paralysis, Abducens nerve paralysis

Received May 29, 2023. Received revised August 21, 2023. Accepted for publication September 8, 2023.

Introduction

Moebius syndrome is a rare disorder widely recognized as "congenital, uni- or bilateral, non-progressive facial weakness with limited abduction of the eye(s)".[1] Individuals affected with the syndrome usually are unable to smile, close their mouth, and chew. Moebius Syndrome can also be associated with other cranial nerves (CN) palsies, including CNs XII, X, IX, III, VIII, V, IV, and XI, in order of decreasing frequency.[2]

Moebius Syndrome was first identified by A. Von Graefe, who described a case of congenital, combined sixth and seventh nerve palsies. However, it was in 1888 that Paul Julius Moebius, a German neurologist, received the honor of the eponym owing to his insightful reports on the clinical features of the ophthalmoplegias associated with Moebius Syndrome.[3] Since then, many newly recognized clinical manifestations associated with Moebius Syndrome have emerged, ranging from musculocutaneous to cardiac and psychiatric complications.[1,4,5] Although the etiology of Moebius Syndrome is vastly unknown, there has been strong speculation that the syndrome may be associated with an embryological disruption of the subclavian artery. Other theories attribute Moebius Syndrome to varying genetic and environmental factors.[6,7] The article aims to assemble and comprehensively present updated literature and recent developments on this condition's clinical features, diagnosis, and management.

Epidemiology

It is rather difficult to assess the epidemiology of Moebius Syndrome owing to a lack of expertise, misdiagnosis, and an absence of regional registries and referral centers.[8] Studies on

[1]Department of Internal Medicine, Ziauddin Medical University, Karachi, Pakistan
[2]Department of Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

Corresponding Author:
Sajjad Ali, Department of Internal Medicine, Ziauddin Medical University, 4/B, Saharah-e-Ghalib, Block 6, Clifton, Karachi – 75600Sindh, Pakistan.
Email: sajjad110@live.com

the Dutch population revealed that the prevalence of Moebius Syndrome was 0.002% (4/ 189,000) in 1996. A recent survey by Carta et al. revealed that the prevalence of Moebius Syndrome was 0.3 per 100,000 live births. Moreover, there seems to be no gender prediction associated with Moebius Syndrome nor any weather or climatic factors that may contribute to the pathogenesis of Moebius Syndrome. It is noteworthy that the average age of diagnosis of Moebius Syndrome has decreased from 3.4 years to 2.2 years since the introduction of MDC at the Bethseda convention in 2007, allowing favorable outcomes through early intervention.[8]

Classic Features & Newly Recognised Manifestations

Clinical researchers and doctors have documented the clinical manifestations of Moebius Syndrome over the years. With the advent of time, Moebius Syndrome has presented with several other features with the classic clinical phenotype; the paralysis of CN VII (96%), with either total, partial, unilateral, or bilateral, and of CN VI (85%), now occurring with a myriad of newly recognized manifestations.[1]

As discussed above, the key feature of Moebius Syndrome is its facial symptoms.[9] Individuals with Moebius Syndrome mainly exhibit weakness or complete paralysis of the facial muscles leading to difficulty swallowing and sucking, underdeveloped speech, and facial expressions.[1]

Similarly, the involvement of CNs III, IV, VI, and VII lead to deficits in ocular motility and neuro visual function.[1] In addition, patients often suffer from delayed onset of lacrimation (between 4-6 months) and may later experience the crocodile tear phenomenon[10] and dry eyes,[11] and epiphora.[12] Other oculomotor defects include strabismus, esotropia, V-pattern, abduction limitation, and refractive errors, with compound hyperopic astigmatism being the most common type.[13] Carta et al. identified three distinct patterns of ophthalmologic manifestations in Moebius Syndrome. Pattern A (41% of cases) consists of orthotopia in the primary position with a complete defect in both abduction and adduction ocular movements. The most prevalent Pattern B (50% of cases) presents as a large-angle esotropia, crossed fixation, and a relative sparing of convergence and adduction. Moreover, Pattern C (9% of cases) presents a large-angle exotropia in the primary position with torticollis, absence of convergence, and vertical eye misalignment. These patterns may each characterize the different types of injuries in the CN VI nucleus and fasciculus.[10]

Interestingly Ventura et al. found similar demographics in their study, with the prevalence being 31.8%, 39.4%, and 16.66% for Patterns A, B, and C, respectively.[14] Ventura et al. also observed an unusual eye movement pattern in their sample where the patients presented with gaze-evoked nystagmus on upward gaze and an excyclotorsion during the cover test.[14] Other prevalent conditions include bilateral epicanthus and unilateral amblyopia, abnormal binocular vision, stereopsis, suppressive scotoma, incomplete or defective closure of the eyelids (lagophthalmos),[1,4,10] and photophobia.[1] Interestingly often in cases of lagophthalmos, no corneal damage is observed due to a preserved bells phenomenon.[10]

Moebius Syndrome has further presented with musculoskeletal deformities. These include clubfoot being the most common symptom, with other features including syndactyly, brachydactyly, syndactyly, ectrodactyly, acheiria, arthrogryposis, kyphosis, scoliosis, kypholordosis, absent or rudimentary fingers or toes, and rib defects.[1] However, it is interesting to note that familial cases of Moebius Syndrome usually lack musculoskeletal involvement, with their risk of transmission roughly 2%.[2,15] Moebius Syndrome patients may also present with orthodontic manifestations. Magnifico et al. reported a high prevalence of lip and palatal clefts, diminished temporomandibular movements, malocclusion with micrognathia, and excessive maxillary development in Moebius Syndrome patients.[16] Other orthodontic manifestations may include microstomia, tongue malformation, high-arched palate, cleft lip or cleft palate, bifid uvula, and dental malocclusion.[17] Moebius Syndrome is also markedly characterized by an overall global delay at one year and impaired speech, motor, and emotional maturity at two years, normalizing when the child turns three. Even so, weak cognitive function, poor hand-eye coordination, and an average IQ may persist until age five. Lifelong cognitive impairment has also been retained in 10% of the affected children.[1]

Apart from the well-established manifestations discussed above, several new associated presentations have been presented in recent years. Table 1 highlights some of the prominent manifestations associated with Moebius Syndrome that have been reported between 1980 to 2022.

Poland Syndrome Coexisting with Moebius Syndrome

Poland Syndrome is characterized by unilateral aplasia of the chest wall (pectoralis major), symbrachydactyly, and webbed fingers on the same side.[9] Other accompanying features of this syndrome are hypoplasia of the forearm and/or breast, agenesis of the nipple, rib cage deformities, bilateral epicanthus, and talipes equinovarus. Stark and Sugarman first identified the co-occurrence of Moebius Syndrome and Poland Syndrome in 1973.[29] Statistically, the prevalence of Moebius Syndrome with Poland Syndrome is 1:500,000. The two diseases' occurrence could indicate similar etiologies; however, no substantial link has been established. Moebius Syndrome has been linked with various etiologies, whereas Poland Syndrome is increasingly considered to have a more sporadic origin.[9] Both syndromes influence the cosmetic outlook of the affected patient and hence have a similar treatment approach. Moebius Syndrome treatment options span around surgical procedures, and Poland Syndrome requires reparation of the chest wall to reduce morbidity and increase functionality. Depending on the gender, reconstruction surgery also includes mammoplasty. Both syndromes aim to achieve symmetry and improve quality of life.[9]

Table 1. Associated Clinical Manifestations of Moebius Syndrome Observed Between 1980 to 2022.

Study	Age/ Gender	Cranial Nerves Involved	Clinical Manifestation	Associated Findings
CARDIOVASCULAR PATHOLOGY				
Thapa et al. (2009)[18]	2y/M	VI, VII	Atrial-Septal Defect (ASD)	Ejection systolic murmur of Grade III/VI, fixed split-second heart sound, and 6 mm ostium secundum defect seen on CT scan
Bosch-Banyeras et al. (1984)[19]	ab/M	VI, VII, IX, X	Dextrocardia in PS-MBS	No murmurs detected, Isolated dextrocardia on ECG & echocardiogram
ENDOCRINE PATHOLOGY				
Hashimoto et al. (1993)[20]	17y/M	II, VI, VII, VIII	Pituitary dwarfism and Hypoplastic Optic Disc	Highly retarded bone growth, absence of pubertal growth spurt, infantile external genitalia, small-sized thyroid and pituitary glands, low testosterone, low GH provocation test results, and LHrH tests in the prepubertal range. Persistent pupillary membrane and coloboma of the left optic nerve, abnormal left pupil shape, severe left ear deafness, and mild hearing right ear impairment
Kawai et al. (1990)[21]	15y6 m/ M	II, III, VI, VII	Hypogonadotropic hypogonadism and peripheral neuropathy	Failure of the adolescent growth spurt, secondary sexual characteristics absent, hypogonadism, Low levels of LH, FSH, and testosterone. Lower motor neuron lesion, subnormal motor neuron conduction velocity in lower limbs, mild subsarcolemmal aggregation of mitochondria.
Ichiyama (1995)[22]	19 m/F	III, VI, VII	Premature thelarche	Thelarche at ten months and FSH predominant response to LHrH
OTHER				
Tanaka et al. (2022)[23]	ab/F	VI, VII	Neurogenic bladder	At birth - urinary retention since birth, recurring urinary tract infection. Two months of age - bladder wall irregularity, hydronephrosis, and bilateral grade 5 vesicoureteral reflux. At two years of age - detrusor overactivity and detrusor-sphincter dyssynergia.
John et al. (2013)[24]	15 m/M	VI, VII, VIII	Dandy-Walker variant and complete agenesis of the corpus callosum.	Corpus callosum agenesis with inferior vermian hypoplasia with the prominent fourth ventricle.
Buccoliero et al. (2011)[25]	1y/M	VII	Splenogonadal fusion and intestinal intussusception.	Abdominal distension, vomiting, bloody stools, ileo-ileal intussusception, cryptorchidism.
Freire et al. (2019)[26]	ab/F	VI, VII	Ankyloglossia Superior syndrome.	Tongue hypomobility, restricted mouth opening (<10 mm), loss of continuity of the palatal shelf, and absence of oral–nasal communication.
Viteri et al. (2021)[27]	2y/M	VI, VII, IX	Splenogonadal fusion associated with Poland syndrome.	Splenogonadal fusion, visible mass in the left inguinal region.
Preis et al. (1996)[28]	3y/F	VI, VII	Goldenhar anomaly with MBS and Poland syndrome, hypoglossal, and hypodactyly anomalies.	Bilateral anotia, epidermoid, submucous cleft palate, spina bifida occulta at L5, ventricular septal defect, shortened tongue tip, hypodactyly, hypodactyly of the left hand with absent distal phalanges and an epidermal cyst on right conjunctiva.
Chen et al. (2021)[17]	21y/M	VII, VIII	Early eruption of deciduous teeth.	The patient had an early eruption of his deciduous teeth at the age of 2 months. He also had other orthodontic manifestations, including crowded dentition, swollen and hyperplastic gingiva, dental calculus of degree I, impacted teeth, dental caries, and a high-arched palate.

Abbreviations: ab, at birth; d, days; m, months; y, years; M, male; F, female.

Etiology & Pathogenesis

Although the classic features of Moebius Syndrome are associated with the agenesis or malformations of CN VI and CN VII nuclei, its etiology and pathogenesis are largely unknown.[30] The two most widely accepted mechanisms are described below. These are genetic causes and ischemic insults during embryogenesis.[1]

Etiology

Genetic Basis. It is difficult to determine the exact cause of Moebius Syndrome due to its multifaceted presentations and manifestations. One study looked for genetic aberrations in Moebius Syndrome patients, focusing on any de novo mutations, and found that allelic defects in two genes, the PLXND1 and REV3L genes, were causative of a significant portion of the etiologies.[31] Another significant set of genes implicated in Moebius Syndrome pathogenesis were labeled the homeobox family of genes, particularly HOXA1, HOXB1, and SOX14.[32] The likely loci involved in the aberrant homeobox genes that might be causative of Moebius Syndrome include 1p22, 3q21-22, 10q21.3-q22.1, and 13q12.2-1345. In this connection, some have even been labeled as Moebius Syndrome 1 (13q12.2-q13), Moebius Syndrome 2/ Hereditary Congenital Facial Paresis 1 viz. HCFP1 (3q21-q22) and Moebius Syndrome 3 or HCFP2 (10q21.3-q22.1).[33] Although most cases of Moebius Syndrome are sporadic, it must be noted that some familial trend has also been observed, including autosomal dominant, recessive, and X-linked recessive inheritance.[8]

Ischemic & Embryonic Basis. Many researchers have reasoned that the different sites of defects found in Moebius Syndrome collectively point to a fault in the embryological stages.[6] It is suspected that ischemic damage to the major blood supply of the developing second pharyngeal arch and the vertebral-basilar system leads to lasting morphological defects that are representative of Moebius Syndrome. Hemorrhage, stenosis, or thrombosis in the veins of the second pharyngeal arch and facial arteries can purportedly lead to ischemia in these regions, resulting in underdeveloped cranial nerves, the hallmark of Moebius Syndrome.[6] Another study proposes that interrupted blood supply in the developing subclavian arteries might also be involved in the pathogenesis of Moebius Syndrome and may lead to defects such as aplasia of the pectoralis major, Sprengel anomaly, and transverse limb defects.[6] These vascular insults may be attributed to hypothermic and hypoxic episodes during embryogenesis.[2]

Moreover, evidence suggests an association between these vascular insults and prenatal exposure to teratogens such as alcohol, cocaine, and ergotamine.[2] This has further been backed by evidence that teratogenesis and abortifacients correlate to a higher incidence of Moebius Syndrome. Thalidomide, a drug well known for its teratogenic effects, has been known to not only harm the formation of the eye but also to disrupt the formation of cranial nuclei in the brain stem, resulting in hypoplasia of the CN VI and VII, a key feature of Moebius Syndrome.[7] Several studies have shown a strong correlation between misoprostol usage and Moebius Syndrome, which has been reliably corroborated by decades of research.[14,34] Furthermore, one key factor supporting this view is that the affected structures commonly originate between 23 to 46 days of embryonic life, suggesting the embryologic origin of Moebius Syndrome might be a stronger overall argument as this is also the period in which teratogenesis affects the embryo the most.

Moreover, there have been rare cases that report a link between the usage of artificial reproductive technologies such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ISCI) and the occurrence of Moebius Syndrome.[35] An interesting finding was made by Pederson et al., who, in a study on five Moebius Syndrome patients, reported that two patients were born to mothers with gynecological anomalies (unicornuate/ bicornuate uterus).[36] However, without conclusive information, it is impossible to state the exact etiology of Moebius Syndrome.

Diagnosis

As the Moebius Syndromes definition varies, so does its diagnostic criteria.[2] Most clinicians diagnose Moebius Syndrome in the presence of CN VII and VI palsies that can be either bilateral or unilateral and partial or complete.[2] This aligns with the recent approach, focusing on defining limits on what constitutes Moebius Syndrome and demarcating it from other unrelated diseases such as Duane syndrome, non-congenital abducens nerve palsy, and metabolic neuropathy. In 2007, an international group of researchers at the First Scientific Conference on Möbius Syndrome In Bethesda, Maryland, set the minimum diagnostic criteria (MDC) for Moebius Syndrome as "*a congenital, non-progressive facial weakness, coupled with the inability to abduct one or both eyes*".[10,37] "Patients with symptoms similar to Moebius Syndrome who do not meet the MDc may be termed as Mobius-like cases".[10] With a working MDC, it has become easier to sort through the literature and identify cases of Moebius Syndrome, making it easier for researchers to develop newly recognized classification and grading systems. However, it is essential to consider the array of more unique features presented after meeting the MDC before concluding.

Recent studies are now paying attention to possible causative genetic patterns for diagnosing Moebius Syndrome.[31] Diagnostics and imaging modalities, such as electromyography, nerve conduction studies, ultrasonography, and magnetic resonance imaging (MRI), can now be employed when diagnosing Moebius Syndrome. Electromyography (EMG) and nerve conduction studies (NCS) are very effective in diagnosing and differentiating Moebius Syndrome from other neuropathic and myopathic causes of congenital facial weakness.[38] Regarding imaging, MRI provides excellent visualization of abnormalities in cranial nerves and related structures.[39] The bilateral absence

of facial and abducens nerves can be considered a characteristic feature of MRI.[39]

Other commonly reported anomalies in imaging include:

(i) Brainstem hypoplasia accompanied by straightening of the floor of the fourth ventricle
(ii) Calcification in pons in the region of the nuclei of cranial nerve VI,
(iii) Missing hypoglossal eminence at the medulla
(iv) Hypoplasia of the cerebellum may be accompanied by hypoplasia of extraocular muscles.[39]

.

Pedraza et al. documented three cases of patients with Moebius Syndrome and their radiological findings. MRI findings of all three patients reported alterations in brainstem morphology without abnormal signal intensity. This finding reflects hypoplasia of the pons and medulla, supporting the diagnosis.[40] However, most studies reporting MRI findings concerning Moebius Syndrome used conventional brain MRI methods; hence, these reports are restricted to cerebellum and brainstem morphology and do not comment on the visualization of the corresponding cranial nerves.[41] In contrast, Verzijl et al. used high-resolution three-dimensional T1 (MP rage) and T2 (CISS) weighted MRI scans to visualize segments of the facial nerve and reported its absence in a sample of six patients.[42] A similarly comprehensive study by Kim et al. in a sample of nine patients concluded that the abducens and the facial nerves were absent bilaterally in most patients (n = 6) with Moebius Syndrome. However, the degree of facial palsy and limited abduction were often asymmetric and variable.[41]

Moreover, to the researchers' surprise, despite showing a bilateral absence of the abducens nerve on MRI, one of the patients displayed a unilateral limitation in adduction.[41] This could be due to aberrant innervation by other cranial nerves.[41] This shows that it is impossible to confirm the bilaterality of Moebius Syndrome through clinical examination, further highlighting the need for inculcating the use of MRI in the workup of suspected cases of Moebius Syndrome.[41] Recently, Sadeghi et al. used the highly sensitive and specific DTI (diffusion tensor imaging)-driven tensor-based morphometry to identify small areas of volumetric abnormalities in the brain, characteristic of Moebius Syndrome.[30]

Evidence suggests that diagnosing Moebius Syndrome during the ante-natal period is possible. For example, polyhydramnios and decreased respiratory movements due to maldevelopment or destruction of brainstem nuclei can be an indicator.[2] Yoon et al. observed this in their case of Moebius Syndrome with polyhydramnios, accompanied by decreased fetal motion and no respiratory movements. The neonate's CT scan later reported hypoplasia of the brain stem with numerous calcifications in the medulla, pons, and mid-brain, characteristic of Moebius Syndrome.[43] A case by M. Sherer et al. reported a normal amount of amniotic fluid and normal fetus swallowing at early gestation but with massive polyhydramnios during the latter part of pregnancy, along with micrognathia, absent mandibular movement, and a non-visualized stomach, which strongly points towards a late in-utero development of Moebius Syndrome.[44] Recently, Nguyen et al. were able to use antenatal MRI imaging to demonstrate several features characteristic of Moebius syndrome, such as the fattened posterior aspect of the pons & medulla and tectal beaking, in a fetus who was later diagnosed with Moebius syndrome.[45] Genetic testing through amniocentesis may be done in cases of polyhydramnios and a family history of Moebius Syndrome to investigate further a pathogenic variant in the PLXND1 / REV3L / homeobox genes.[46]

Grading and Classification

A study by Abramson et al. presented one of the systems often used to classify and grade Moebius Syndrome.[47] The authors recognized five commonly affected sites, grading each depending on the abnormalities present or their severity (as shown in Table 2). The development of such a grading system gives us several other advantages, including the ease of analysis of management procedures and comparing patient groups.[47]

Table 2. the System Devised by Abramson et al. to Classify the Extent of MBS Marked by Morphological Deformities.

	0	I	2	3	Bilateral
C (Cranial Nerve)	Incomplete CN VII hypoplasia	Incomplete CN VI and VII hypoplasia	Complete CN VI and VII hypoplasia	Additional nerve hypoplasia	If bilateral and equal, add B after the numeral (eg, 2B)
L (Lower extremity)	No deformities	Talipes equinovarus, syndactyly, ankylosis	Absent phalanges	Longitudinal or transverse defects	Not applicable
U (Upper extremity)	No deformities	Hypoplasia of fingers or failure of differentiation	Ectrodactyly	Longitudinal or transverse failure of formation	Not applicable
F (Facial structural anomaly)	No deformities	Cleft palate	Micrognathia	Microtia, microphthalmia, abnormal joint, etc.	Not applicable
T (Thorax)	No deformities	Scoliosis	Pectoral hypoplasia/ Breast anomaly	Chest wall deformity, breast, or pectoral hypoplasia	Not applicable

However, it may be argued that the defects within Moebius Syndrome are too diverse to be classified in one system. It will also be challenging to introduce a definitive grading and classification system until the debate on the etiology of Moebius Syndrome is settled. Perhaps the inclusion of the findings from modern diagnostic modalities such as MRI will help develop a more inclusive and accurate classification system.

On the other hand, Picciolini et al. have proposed a more functionality-based approach, utilizing the *"International Classification of Functioning Children and Youth"* (ICF-CY) published by the World Health Organization (WHO). ICF-CY includes patient functioning, disability, participation in daily activities, and the impact of the familial and social environment that may affect a patient instead of focusing solely on the morphology. ICF-CY allows care providers to assess and integrate complex signs and functions in Moebius Syndrome patients. These include motor skills, feeding, language, communication, and cognitive function. Such a protocol may allow ease in defining treatment plans and planning interventions on an individual basis, given the frequent and vast impairments the patients may face in their day-to-day life.[1]

Differential Diagnosis

Several conditions may present features like Moebius Syndrome, sometimes even concurring. Therefore, it is essential to rule them out while making a diagnosis. Table 3 mentions the genetics and inheritance patterns of different conditions they may present with congenital facial weakness, while Table 4 mentions several other differential diagnoses for Moebius Syndrome while accounting for the various Moebius Syndrome features presented over time.

Facial Mimicry and Social Implications

The clinical features of Moebius Syndrome can considerably affect a patient's normal functioning and social interactions. The marginalizing behavior of people, which starts at an early age, may result in further detrimental effects, possibly leading

Table 3. Differential Diagnosis of Congenital Facial Weakness Disorders.

NEUROGENIC CONGENITAL FACIAL WEAKNESS							
Disorder	Athabaskan brainstem dysgenesis syndrome/ Bosley-Salih-Alorainy syndrome[48]	Congenital fibrosis of the extraocular muscles 3A with or without extraocular involvement[49]	CHARGE syndrome[50]	Hereditary congenital facial paresis type 3 [51]	Moebius syndrome[52]	Oculo-auriculo-vertebral spectrum[53]	
Gene	*HOXA1*	*TUBB3*	*CHD7*	*HOXB1*	*PLXND1, REV3L*	Unknown	
Moi	AR	AD	AD	AR	IC; AD (rare)	IC; AD (rare)	

NEUROMUSCULAR JUNCTION CONGENITAL FACIAL WEAKNESS			
Disorder	Congenital myasthenic syndrome 9 associated with acetylcholine receptor deficiency[54]	Congenital myasthenic syndrome 10 [55]	Congenital myasthenic syndrome 11 associated with acetylcholine receptor deficiency[56]
Gene	*MUSK*	*DOK7*	*RAPSN*
Moi	AR	AR	AR

MYOPATHIC CONGENITAL FACIAL WEAKNESS										
Disorder	Carey-Fineman-Ziter syndrome[57]	Central core disease/ Multiminicore disease[58]		Centronuclear/ myotubular myopathy[59]			Congenital myopathy- Zaharieva et al. [2016][60]		Facioscapulohumeral muscular dystrophy[61]	
Gene	*MYMK*	*RYR1*	*SEPN1*	*BIN1*	*DNM2*	*MTM1*	*SCN4A*		*DUX4*	*SMCHD1*
Moi	AR	AD, AR	AD, AR	AR	AD	XLR	AR		AD	AD

MYOPATHIC CONGENITAL FACIAL WEAKNESS								
Disorder	Myotonic dystrophy, type 1 [62]	Native American myopathy[63]	Nemaline myopathy[64]					*ZC4H2*-associated rare disorders[65]
Gene	*DMPK*	*STAC3*	*ACTA1*	*KLHL40*	*NEB*	*TPM2*	*TPM3*	*ZC4H2*
Moi	AD	AR	AD, AR	AR	AR	AD	AD, AR	XLR

MIXED/UNKNOWN CONGENITAL FACIAL WEAKNESS				
Disorder	Asymmetric crying facies[66]	*KAT6B* disorders[67]	Marden-Walker syndrome[68]	Nablus mask-like facial syndrome[69]
Gene	22q11	*KAT6B*	*PIEZO2*	8q22.1
Moi	IC; AD	AD	IC; AD	AD

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; IC, isolated cases.

Table 4. Differential Diagnoses for Moebius Syndrome.

Condition	To rule out
Cerebral Palsy (CP)	Symptoms of CP are exhibited by a group of disorders that affect the individual's ability to move, maintain balance, and posture. Apparent developmental delays, abnormal floppy (or stiff) muscle tone, and an abnormal posture are signs of CP. In addition, a combination of a CT scan, MRI, EEG, and genetic testing can be done to differentiate between Moebius Syndrome and CP.[70]
Metabolic Myopathies	Individuals with metabolic myopathies lack the enzymes needed to provide energy that makes muscles contract. Symmetric proximal muscle weakness, malaise, fatigue, and paresthesia are also possible symptoms. Hence, a muscle tissue biopsy and electromyography or specific blood tests for markers can be done to rule it out.[71]
Acquire facial nerve dysfunction (Bell's Palsy or isolated nerve injury)	EMG and NCS will be able to detect the presence of nerve damage since peripheral neuropathy can alter how the brain reacts to stimuli and cause symptoms like numbness, tingling, sharp or buzzing sensations. At the same time, Bell's Palsy may be distinguished from Moebius Syndrome by its sudden onset, potential recovery, and history of nerve damage in other acquired CN-7 neuropathies.[72,73]
Acquired facial palsy from a traumatic delivery	These usually present with a history of macrosomia instrumental delivery and facial presentation. In addition, a nerve conduction test may be incorporated to confirm the presence, narrow down the location of the nerve injury, and determine the severity.[74,75]
Velo-cardio-facial syndrome(VCFS) /DiGeorge syndrome	These are caused by a deletion at 22q11.2. The diagnosis is based on the presence of its distinct clinical features along with other symptoms. The differential features from Moebius Syndrome include cleft palate and cardiac anomalies, thymic hypoplasia, hypoparathyroidism, and cardiac defects . Patients tend to have a long face with a prominent upper jaw, an underdeveloped lower jaw, low-set ears, and a prominent nose with narrow nasal passages. Moreover, their association with immune disorders such as T-cell dysfunction further differentiate them from Moebius Syndrome.[76]
Duane syndrome	Diagnosis is made clinically, usually by the age of 10. The symptoms include limited horizontal eye movement, retraction of the globe, crossing (or misalignment) of the eyes, and a compensatory turning of the head. In addition, Duane syndrome patients usually lack facial nerve palsy features.[77]
Hanhart syndrome	Physical features that help distinguish Hanhart syndrome include hypoglossia, hypodactylia, peromelia, and micrognathia.[78]
Charlie M syndrome	It is a disorder of craniofacial dysmorphism that consist of a broad nose, large set ears, and microcephaly. It is characteristically known as a claw hand deformity and can be ruled out by its physical findings.[79]
Klippel-Feil anomaly	The diagnosis is based on the patient's symptoms, clinical examination, and imaging studies. It is a fusion of two or more spinal bones in the neck, a short neck, a low hairline, and torticollis.[80]

to a lack of confidence, impaired holistic development, and social withdrawal, often leading to severe psychiatric illnesses.[33,81] Facial and automatic mimicry plays a central role in emotional processing and social interactions. Upon viewing a person's facial expression, an individual's typical response, often non-conscious, is activating neural processes to replicate the perceived expressions. This leads to a better understanding of their emotions, allowing empathy and improved social interactions, a phenomenon known as "facial mimicry." This process becomes more accurate with age.[33] Thus, the inability of Moebius Syndrome patients to replicate facial expressions and cues leads them to have difficulty identifying and processing emotions. This, coupled with speech difficulties, often leads to them being perceived as unintelligent or unfriendly. This is supported by several studies where the artificial inhibition of facial movements in normal individuals led to their decreased ability to recognize emotions.[33]

Moreover, due to facial palsy, Moebius Syndrome patients cannot give facial cues preventing them from participating in empathetic communications.[82] This, along with instances of social rejection, may lead to limited social interactions, adversely affecting an individual's psychological and social development.[33] In addition to the aforementioned, a quantitative study by Briegel on Moebius Syndrome patients reported a slight tendency towards increased anxiety and depression and overall low satisfaction with life with low success orientation and high incidence of suicidal thoughts.[83] Similar reports were published by VanSwearingen et al. on patients with facial neuromuscular disorders.[84]

For this reason, many intervention programs have been proposed to enhance speech and oral competence and improve their quality of life. These include surgical and medical interventions, as well as different therapeutic and rehabilitative programs such as respiration control, neuromuscular training, massage,

meditation-relaxation, and psychological and communication strategy interventions, including but not limited to the positively indicated post-surgery FIT-SAT therapy regimen.[33,81]

Thus, it is crucial to ensure adequate support, counseling, and clinical intervention for facial palsy and other features found in Moebius Syndrome patients from an early age to provide them relief and improve their overall quality of life. In addition, it is recommended to consult psychologists throughout the patient's lifetime with Moebius Syndrome and to evaluate their mental health from time to time.[33]

Psychiatric Evaluations & Clinical Diagnosis

It is vital to recognize that the physical limitations of Moebius Syndrome patients may adversely affect their psychiatric and clinical evaluations. As suggested by Jacques et al., it might be difficult for the caregiver to effectively communicate with Moebius Syndrome patients owing to a fixed gaze, blank expressions, and speech impediment frequently observed in Moebius Syndrome.[85] This may cause a misdiagnosis of a patient's condition leading to improper treatment, which may aggravate the patient's condition or even give rise to other complications. The article also stressed the importance of psychoeducation regarding non-verbal forms of communication prior to psychiatric evaluations in patients with Moebius Syndrome.[85] Another study revealed that it is common for physicians and psychiatrists to wrongly diagnose Moebius Syndrome patients with mental disorders, with actual mental disorders being present in only 14% of the cases.[81]

Treatment, Surgical and Therapeutic Interventions

Moebius Syndrome has widespread effects on the patient's health and therefore requires a multisystemic approach to treatment. As such, much care is needed to ensure that each deficiency is addressed in a manner that does not worsen a patient's lifestyle. Therefore, a multidisciplinary approach is required.

Two of the most life-threatening outcomes of Moebius Syndrome can be severe dysphagia and aspiration pneumonia.[86] Therefore, high-risk patients have been suggested to follow a special diet to minimize the risks.[86] Moreover, in some instances, due to a compromise of the airway, an elective tracheostomy may be beneficial for patients to allow for easier breathing and airway clearing.[86] Furthermore, it must be noted that restoring even a small degree of voluntary facial movements can reap massive improvements in verbal and non-verbal communication and would solve several everyday problems, including eating, drinking, and facial animation. Facial muscle atrophy or aplasia is often treated by transplantation of a segment of the gracilis muscle of the leg by the procedure called "Smile surgery".[81] Innervation to this transplanted muscle segment is usually from neighboring parts of the facial nerve, which are not affected by Moebius Syndrome or the contralateral facial nerve. The graft is vascularized by forming anastomoses between facial vessels and the Vena comitans of the Gracillis.[81] Care must be taken to preserve the facial aesthetics of the patients during the procedure. In a study conducted on 12 patients with Moebius Syndrome or Moebius Syndrome-like presentation, 83.4% of the patients revealed satisfaction with the functional and aesthetic outcomes of the surgery.[81] However, it contrasts with several other studies. Usually, between three to six months after surgery, the transplanted muscle makes its first contractions with several more months of physiotherapy and neurorehabilitation before the patient can smile again.[33] Even after, the smile is often not symmetric, owing to the involvement of the trigeminal nerve in sensory and motor functions of the face.[33] A newly recognized neurorehabilitation treatment called "FIT-SAT", which utilizes the presence of the "mirror neuron system" and the synergistic coordination between the mouth and the hand, has been proven to help achieve a more natural and spontaneous smile post-operation and an overall improved facial functioning as compared to traditional methods such as teeth clenching exercises.[33] FIT-SAT allows effective rehabilitation in the comfort of the patient's homes through the provision of audio-visual lectures.[87] It must also be noted that the patient's motivation drive plays a significant role in the rehabilitation process.[88]

It is important to note that the lagophthalmos in Moebius Syndrome can lead to dry eyes, keratitis, or more severe complications such as corneal ulceration, perforation, and endophthalmitis. Mild cases are usually managed using lubricants and hygienic measures. However, surgical intervention may be required in severe or refractory cases.[89] The most common procedure is a gold-weight implant in the upper eyelid.[90] This, coupled with muscle grafts (e.g., platysma muscle), can provide permanent relief.[89] Tarrsorhaphy is the treatment of choice for lower eyelid dysfunction.[90] Other options include muscle or fat transfers and fascia slings.[9,88] Staples et al. have recently proposed a new method of using the deep temporal nerve for muscle graft transfer.[91] Magli et al. documented the successful long-term management of lagophthalmos through blepharoplasty using different grafts.[92]

Early diagnosis and corneal protection are also important to allow for positive outcomes of strabismus correction. Initially, botulism injections into the medial rectus for abducens nerve palsy prevent contractures, allowing conjugate gaze. Later, surgical intervention would allow for definitive long-term management.[93,94] Different surgical options are available for the different patterns of strabismus. These include medial rectus recessions, combined medial rectus muscle recession, lateral rectus muscle resection, and the transposition of vertical or/and inferior rectus muscles.[95,96] All procedures have shown successful outcomes and improved abduction function[97] in different studies.[95,96,98] In addition, double-augmented vertical recti transposition has been proven particularly effective in cases of large angle deviations.[96] Early intervention further allows positive outcomes, such as the development of some degree of binocularity.[95,96] Moreover, medial rectus recessions alone may be considered a first-line treatment given the low incidence of complications such as anterior segment ischemia and new onset vertical strabismus that may occur in other procedures.[95]

Transconjunctival injection of botulinum toxin into the lacrimal gland is known to treat crocodile tears successfully. However, surgical options, including Corda tympani resection and lacrimal gland temporal lobe resection, are rarely used due to complications.[99] In cases of epiphora, lateral eyelid tarsal strip procedure (in cases of lid laxity), dacryocystorhinostomy, or Jones tube insertion may improve tear drainage.[12]

The course of action for oropharyngeal defects caused by Moebius Syndrome depends on the extent of the malformation. Francoli et al. and Sensat et al. provide an excellent account of treating their patients with orthodontic manifestations of Moebius Syndrome.[100,101] Treatments may vary widely in such cases, although surgical procedures have long been performed with notable success. However, using a prosthesis in the oropharyngeal cavity is generally preferable over invasive, reconstructive surgery. Moreover, oral healthcare providers must remember that deficient or deformed digits, if present, can cause further trouble with oral hygiene.[101]

The widespread nature of defects in Moebius Syndrome means that it is challenging to address all of the issues with surgery. It is essential to utilize clinical and electrophysiological examinations to identify which gross structures are most dysfunctional and to what extent their dysfunction is caused by loss of innervation, as documented by Terzis et al.[102] Their study also presents a comprehensive treatment plan based on findings, which can provide a blueprint for researchers and doctors alike.[102] More conservative treatment measures may prove effective in helping patients adapt to their lifestyle, though they may not be curative or significant in the case of severe congenital deformities. Plastic surgery may be recommended in a few cases, contingent on the patient's volition.

Conclusion

The rarity of Moebius Syndrome, its strong links with other syndromes like Poland syndrome, and an ever-growing array of clinical features have historically proven barriers to understanding the syndrome, leading to misdiagnosis and poor management. By furthering awareness of the intricacies of this condition, it is hoped that physicians better understand treatment options and newly recognized diagnostics are incorporated into management. Moreover, as the instances of this syndrome are few and far between chronologically, it is essential to have a review of literature available for easy reference, along with an emphasis on reporting any new occurrences. Moebius Syndrome may be more readily understood in the discussion and dissemination of literature across almost two centuries. This will hopefully spark more research into the unknown causes of the syndrome.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sajjad Ali https://orcid.org/0000-0002-8024-5942

References

1. Picciolini O, Porro M, Cattaneo E, et al. Moebius syndrome: Clinical features, diagnosis, management and early intervention. *Ital J Pediatr*. 2016;42(1):56. https://doi.org/10.1186/s13052-016-0256-5
2. Singham J, Manktelow R, Zuker RM. Möbius syndrome. *Semin Plast Surg*. 2004;18:39-45. https://doi.org/10.1055/s-2004-823122
3. Sogg RL. Congenital facial diplegia syndrome of Möbius: A case report. *Arch Ophthalmol*. 1961;65(1):16-19. https://doi.org/10.1001/archopht.1961.01840020018004
4. Verner A, Agarwal-Sinha S, Han FY. Möbius syndrome with cardiac rhabdomyomas. *Ophthalmic Genet*. 2018;39(3):373-376. https://doi.org/10.1080/13816810.2017.1423336
5. Strömland K, Sjögreen L, Miller M, et al. Mobius sequence–a Swedish multidiscipline study. *Eur J Paediatr Neurol*. 2002;6(1):35-45. https://doi.org/10.1053/ejpn.2001.0540
6. Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. *Am J Med Genet*. 1986;23(4):903-918. https://doi.org/10.1002/ajmg.1320230405
7. Miller MT, Ventura L, Strömland K. Thalidomide and misoprostol: Ophthalmologic manifestations and associations both expected and unexpected. *Birth Defects Res A Clin Mol Teratol*. 2009;85(8):667-676. https://doi.org/10.1002/bdra.20609
8. Carta A, Favilla S, Calzetti G, et al. The epidemiology of Moebius syndrome in Italy. *Orphanet J Rare Dis*. 2021;16(1):162. https://doi.org/10.1186/s13023-021-01808-2
9. Chopan M, Sayadi L, Laub D. Mobius syndrome and poland syndrome presenting together in a single patient. *Eplasty*. 2015;15(1) ic12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4338560/ (accessed September 18, 2022).
10. Carta A, Mora P, Neri A, Favilla S, Sadun AA. Ophthalmologic and systemic features in möbius syndrome an Italian case series. *Ophthalmology*. 2011;118(8):1518-1523. https://doi.org/10.1016/j.ophtha.2011.01.023
11. Miller MT, Strömland K, Ventura L. Congenital aberrant tearing: A re-look. *Trans Am Ophthalmol Soc*. 2008;115-6:100. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646435/
12. Alsuhaibani AH. Facial nerve palsy: Providing eye comfort and cosmesis. *Middle East Afr J Ophthalmol*. 2010;17(2):142. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892130/
13. Cronemberger MF, de Castro Moreira JB, Brunoni D, et al. Ocular and clinical manifestations of Möbius' syndrome. *J Pediatr Ophthalmol Strabismus*. 2001;38(3):156-162. https://doi.org/10.3928/0191-3913-20010501-0
14. Ventura BV, Miller MT, Danda D, Carta A, Brandt CT, Ventura LO. Profile of ocular and systemic characteristics in Möbius sequence patients from Brazil and Italy. *Arq Bras Oftalmol*. 2012;75(3):202-206. https://doi.org/10.1590/s0004-27492012000300011
15. MacDermot KD, Winter RM, Taylor D, Baraitser M. Oculofacialbulbar palsy in mother and son: Review of 26 reports of familial transmission within the "Möbius spectrum of defects". *J Med Genet*. 1991;28(1):18-26. https://doi.org/10.1136%2Fjmg.28.1.18
16. Magnifico M, Cassi D, Gandolfini M, Toffoli A, Zecca PA, Di Blasio A. Orthodontics and Moebius syndrome: An

observational study. *Minerva Stomatol*. 2018;67(4):165-171. https://doi.org/10.23736/S0026-4970.18.04095-5
17. Chen B, Li L-X, Zhou L-L. Dental management of a patient with Moebius syndrome: A case report. *World J Clin Cases*. 2021;9(24):7269-7278. https://doi.org/10.12998/wjcc.v9.i24.7269
18. Thapa R, Bhattacharya A. Moebius syndrome with atrial septal defect. *Singapore Med J*. 2009;50(10):1030-1031. https://pubmed.ncbi.nlm.nih.gov/19907896/
19. Bosch-Banyeras JM, Zuasnabar A, Puig A, Català M, Cuatrecasas JM. Poland-Möbius syndrome associated with dextrocardia. *J Med Genet*. 1984;21(1):70-71. https://doi.org/10.1136/jmg.21.1.70
20. Hashimoto N, Sakakihara Y, Miki Y, Kagawa J, Egi S, Kamoshita S. Moebius syndrome associated with pituitary dwarfism and hypoplastic optic disc. *Acta Paediatr Jpn*. 1993;35(2):144-147. https://doi.org/10.1111/j.1442-200X.1993.tb03026.x
21. Kawai M, Momoi T, Fujii T, Nakano S, Itagaki Y, Mikawa H. The syndrome of Möbius sequence, peripheral neuropathy, and hypogonadotropic hypogonadism. *Am J Med Genet*. 1990;37(4):578-582. https://doi.org/10.1002/ajmg.1320370432
22. Ichiyama T, Handa S, Hayashi T, Furukawa S. Premature thelarche in Möbius syndrome. *Clin Genet*. 1995;47(2):108-109. https://doi.org/10.1111/j.1399-0004.1995.tb03938.x
23. Tanaka Y, Maekawa T, Eura R, Hasegawa Y, Kubota M. Neurogenic bladder as a lurking complication in Moebius syndrome. *Brain Dev*. 2022;44(1):73-76. https://doi.org/10.1016/j.braindev.2021.07.006
24. John JS, Vanitha R. Moebius syndrome with Dandy-Walker variant and agenesis of corpus callosum. *J Pediatr Neurosci*. 2013;8(3):210-212. https://doi.org/10.4103%2F1817-1745.123668
25. Buccoliero AM, Messineo A, Castiglione F, et al. Splenogonadal fusion: Exceptional association with Moebius syndrome and intestinal intussusception. *Fetal Pediatr Pathol*. 2011;30(4):220-224. https://doi.org/10.3109/15513815.2010.524686
26. Freire RC, Barbosa APdC, Han MD, Borba AM. Ankyloglossia superior associated with Moebius syndrome: A case report. *J Oral Maxillofac Surg*. 2020;78(1):87-90. https://doi.org/10.1016/j.joms.2019.08.017
27. Cabrera Viteri MI, Acosta Farina D, Morales Mayorga H, Cabrera Johnson M, Albán Castro S. Splenogonadal fusion associated with Moebius and Poland syndromes: First case reported. *Cir Pediatr*. 2021;34(4):219-222. https://pubmed.ncbi.nlm.nih.gov/34606704/
28. Preis S, Majewski F, Hantschmann R, Schumacher H, Lenard HG. Goldenhar, Möbius and hypoglossia-hypodactyly anomalies in a patient: Syndrome or association? *Eur J Pediatr*. 1996;155(5):385-389. https://doi.org/10.1007/BF01955267
29. Sugarman GI, Stark HH. Möbius syndrome with Poland's anomaly. *J Med Genet*. 1973;10(2)192-6. https://doi.org/10.1136/jmg.10.2.192
30. Sadeghi N, Hutchinson E, Ryzin V, et al. Brain phenotyping in Moebius syndrome and other congenital facial weakness disorders by diffusion MRI morphometry. *Brain Commun*. 2020;2(1):fcaa014. https://doi.org/10.1093/braincomms/fcaa014
31. Tomas-Roca L, Tsaalbi-Shtylik A, Jansen JG, et al. De novo mutations in PLXND1 and REV3L cause Möbius syndrome. *Nat Commun*. 2015;6(1):1-9. https://doi.org/10.1038/ncomms8199
32. Kadakia S, Helman SN, Schwedhelm T, Saman M, Azizzadeh B. Examining the genetics of congenital facial paralysis—a closer look at Moebius syndrome. *Oral Maxillofac Surg*. 2015;19(2):109-116. https://doi.org/10.1007/s10006-015-0485-6
33. De Stefani E, Nicolini Y, Belluardo M, Ferrari PF. Congenital facial palsy and emotion processing: The case of Moebius syndrome. *Genes Brain Behav*. 2019;18(1):e12548. https://doi.org/10.1111/gbb.12548
34. Guedes ZCF. Möbius syndrome: Misoprostol use and speech and language characteristics. *Int Arch Otorhinolaryngol*. 2014;18(3):239-243. https://doi.org/10.1055/s-0033-136346
35. Albayrak HM, Tarakçı N, Altunhan H, Örs R, Çaksen H. A congenital cranial dysinnervation disorder: Möbius' syndrome. Turk Pediatri Ars. 2017 Sep 1;52(3):165-168. (accessed September 20, 2022).
36. Pedersen LK, Maimburg RD, Hertz JM, et al. Moebius sequence –a multidisciplinary clinical approach. *Orphanet J Rare Dis*. 2017;12(1):1-11. https://doi.org/10.1186/s13023-016-0559-z
37. Ruge-Peña NO, Valencia C, Cabrera D, Aguirre DC, Lopera F. Moebius syndrome: Craniofacial clinical manifestations and their association with prenatal exposure to misoprostol. *Laryngoscope Investig Otolaryngol*. 2020;5(4):727-733. https://doi.org/10.1002/lio2.377
38. Lehky T, Joseph R, Toro C, et al. Differentiating Moebius syndrome and other congenital facial weakness disorders with electrodiagnostic studies. *Muscle Nerve*. 2021;63(4):516-524. https://doi.org/10.1002/mus.27159
39. Srinivas MR, Vaishali DM, Vedaraju KS, Nagaraj BR. Mobious syndrome: MR findings. *Indian J Radiol Imaging*. 2016;26(4):502-505. https://doi.org/10.4103/0971-3026.195790
40. Pedraza S, Gámez J, Rovira A, et al. MRI Findings in Möbius syndrome: Correlation with clinical features. *Neurology*. 2000;55(4):1058-1060. https://doi.org/10.1212/wnl.55.7.1058
41. Kim N, Kim JH, Kim J-S, Hwang J-M. Möbius syndrome: Clinico-radiologic correlation. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(11):2219-2223. https://doi.org/10.1007/s00417-018-4089-3
42. Verzijl HTF, Valk J, de Vries R, Padberg GW. Radiologic evidence for absence of the facial nerve in Möbius syndrome. *Neurology*. 2005;64(5):849-855. https://doi.org/10.1212/01.WNL.0000152980.92436.D9
43. Yoon K, Yoo SJ, Suh DC, Lee YA, Kim KS, Choe G. Möbius syndrome with brain stem calcification: Prenatal and neonatal sonographic findings. *Pediatr Radiol*. 1997;27(2):150-152. https://doi.org/10.1007/s002470050088
44. Sherer DM, Spafford P. Prenatal sonographic evidence supporting an in utero developmental etiology of Möbius sequence. *Am J Perinatol*. 1994;11(2):157-159. https://doi.org/10.1055/s-2007-994578
45. Nguyen GV, Goncalves LF, Vaughn J, et al. Prenatal diagnosis of Poland-Möbius syndrome by multimodality fetal imaging. *Pediatr Radiol*. 2023(10)2144-2148. https://doi.org/10.1007/s00247-023-05712-8
46. Kuklík M. Poland-Möbius syndrome and disruption spectrum affecting the face and extremities: a review paper and presentation of five cases. *Acta Chir Plast*. 2000;42(3)95-103. https://pubmed.ncbi.nlm.nih.gov/11059047/ (accessed September 20, 2022).
47. Abramson DL, Cohen MM Jr, Mulliken JB. Möbius syndrome: Classification and grading system. *Plast Reconstr Surg*. 1998;102(4):961-967. https://doi.org/10.1097/00006534-199809040-00004
48. Rankin JK, Andrews C, Chan WM, Engle EC. HOXA1 Mutations are not a common cause of Mobius syndrome. *J AAPOS*. 2010;14(1):78-80. 10.1016/j.jaapos.2009.11.007

49. Tischfield MA, Baris HN, Wu C, et al. Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance. *Cell*. 2010;140(1):74-87. 10.1016/j.cell.2009.12.011
50. Zentner GE, Layman WS, Martin DM, Scacheri PC. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. *Am J Med Genet A*. 2010;152A(3):674-686. 10.1002/ajmg.a.33323.
51. Webb BD, Shaaban S, Gaspar H, et al. HOXB1 Founder mutation in humans recapitulates the phenotype of Hoxb1-/- mice. *Am J Hum Genet*. 2012;91(1):171-179. 10.1016/j.ajhg.2012.05.018
52. Miller G. Neurological disorders. The mystery of the missing smile. *Science*. 2007;316(5826):826-827. 10.1126/science.316.5826.826.
53. Heike CL, Luquetti DV, Hing AV. Craniofacial microsomia overview. In: *GeneReviews((R))*. Seattle, WA: University of Washington; 1993-2023.
54. Mihaylova V, Salih MA, Mukhtar MM, et al. Refinement of the clinical phenotype in musk-related congenital myasthenic syndromes. *Neurology*. 2009;73(22):1926-1928. https://doi.org/10.1212/wnl.0b013e3181c3fce9
55. Beeson D, Higuchi O, Palace J, et al. Dok-7 mutations underlie a neuromuscular junction synaptopathy. *Science*. 2006;313(5795):1975-1978. https://doi.org/10.1126/science.1130837
56. Ohno K, Engel AG, Shen XM, et al. Rapsyn mutations in humans cause endplate acetylcholine-receptor deficiency and myasthenic syndrome. *Am J Hum Genet*. 2002;70(4):875-885. https://doi.org/10.1086/339465
57. Di Gioia SA, Connors S, Matsunami N, et al. A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome. *Nat Commun*. 2017;8(1):16077. 10.1038/ncomms16077
58. Jungbluth H, Zhou H, Sewry CA, et al. Centronuclear myopathy due to a de novo dominant mutation in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord*. 2007;17(4):338-345. https://doi.org/10.1016/j.nmd.2007.01.016
59. Nance JR, Dowling JJ, Gibbs EM, Bonnemann CG. Congenital myopathies: An update. *Curr Neurol Neurosci Rep*. 2012;12(2):165-174. https://doi.org/10.1007/s11910-012-0255-x
60. Zaharieva IT, Thor MG, Oates EC, et al. Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or "classical" congenital myopathy. *Brain*. 2016;139(3):674-691. https://doi.org/10.1093/brain/awv352
61. Preston MK, Tawil R, Wang LH. Facioscapulohumeral muscular dystrophy. In: *GeneReviews((R))*. Seattle, WA: University of Washington; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1443/
62. Bird TD. Myotonic dystrophy type 1. In: *GeneReviews((R))*. Seattle, WA: University of Washington; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1165/
63. Horstick EJ, Linsley JW, Dowling JJ, et al. Stac3 is a component of the excitation-contraction coupling machinery and mutated in native American myopathy. *Nat Commun*. 2013;4(1):1952. https://doi.org/10.1038/ncomms2952
64. North KN, Ryan MM. Nemaline myopathy. In: *GeneReviews((R))*. Seattle, WA: University of Washington; 1993-2023. Available from: https://pubmed.ncbi.nlm.nih.gov/20301465/
65. Frints SGM, Hennig F, Colombo R, et al. Deleterious de novo variants of X-linked ZC4H2 in females cause a variable phenotype with neurogenic arthrogryposis multiplex congenita. *Hum Mutat*. 2019;40(12):2270-2285. https://doi.org/10.1002/humu.23841
66. Giannotti A, Digilio MC, Marino B, Mingarelli R, Dallapiccola B. Cayler cardiofacial syndrome and del 22q11: Part of the CATCH22 phenotype. *Am J Med Genet*. 1994;53(3):303-304. https://doi.org/10.1002/ajmg.1320530320
67. Lemire G, Campeau PM, Lee BH. KAT6B disorders. In: *GeneReviews((R))*. Seattle, WA: University of Washington; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114806/
68. McMillin MJ, Beck AE, Chong JX, et al. Mutations in PIEZO2 cause Gordon syndrome, Marden-Walker syndrome, and distal arthrogryposis type 5. *Am J Hum Genet*. 2014;94(5):734-744. https://doi.org/10.1016/j.ajhg.2014.03.015
69. Shieh JT, Aradhya S, Novelli A, et al. Nablus mask-like facial syndrome is caused by a microdeletion of 8q detected by array-based comparative genomic hybridization. *Am J Med Genet A*. 2006;140(12):1267-1273. https://doi.org/10.1002/ajmg.a.31262
70. Sadowska M, Sarecka-Hujar B, Kopyta I. Cerebral palsy: Current opinions on definition, epidemiology, risk factors, classification and treatment options. *Neuropsychiatr Dis Treat*. 2020;16:1505-1518. https://doi.org/10.2147/ndt.s235165
71. Lilleker JB, Keh YS, Roncaroli F, Sharma R, Roberts M. Metabolic myopathies: A practical approach. *Pract Neurol*. 2018(1);18:14-26. https://doi.org/10.1136/practneurol-2017-001708
72. Li R, Liu Z, Pan Y, Chen L, Zhang Z, Lu L. Peripheral nerve injuries treatment: A systematic review. *Cell Biochem Biophys*. 2013;68(3):449-454. https://doi.org/10.1007/s12013-013-9742-1
73. Budenz DL, Wulc AE, Galetta S, Orlin SE. Bell's palsy in Moebius syndrome. *Ophthal Plast Reconstr Surg*. 1991;7(3):187-189. https://doi.org/10.1097/00002341-199109000-00006
74. Al Tawil K, Saleem N, Kadri H, Rifae MT, Tawakol H. Traumatic facial nerve palsy in newborns: Is it always iatrogenic? *Am J Perinatol*. 2010;27(9):711-713. https://doi.org/10.1055/s-0030-1253097
75. Bergman I, May M, Wessel HB, Stool SE. Management of facial palsy caused by birth trauma. *Laryngoscope*. 1986;96(4):381-384. https://doi.org/10.1288/00005537-198604000-00008
76. Shprintzen RJ, Higgins AM, Antshel K, Fremont W, Roizen N, Kates W. Velo-cardio-facial syndrome. *Curr Opin Pediatr*. 2005;17(6):725. https://doi.org/10.1097/01.mop.0000184465.73833.0b
77. Kalevar A, Ong TS, Flanders M. Duane syndrome: Clinical features and surgical management. *Can J Ophthalmol*. 2015;50(4):301-303 https://doi.org/10.1016/j.jcjo.2015.05.005
78. Varal IG, Dogan P. Hanhart syndrome: hypoglossia-hypodactylia syndrome. *Pan Afr Med J*. 2019;32:213. https://doi.org/10.11604/pamj.2019.32.213.17493
79. Jung O, Smeets R, Hanken H, et al. A patient with Charlie M Syndrome: Differential diagnosis of oromandibular limb hypogenesis syndromes. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2016;160(2).310-315 https://doi.org/10.5507/bp.2016.020
80. Frikha R. Klippel-Feil syndrome: A review of the literature. *Clin Dysmorphol*. 2020;29:(1)35. https://doi.org/10.1097/mcd.0000000000000301
81. Bianchi B, Copelli C, Ferrari S, Ferri A, Sesenna E. Facial animation in children with Moebius and Moebius-like syndromes. *J Pediatr Surg*. 2009(11);44.2236-2242 https://doi.org/10.1016/j.jpedsurg.2009.07.038
82. Krueger J, Michael J. Gestural coupling and social cognition: Möbius syndrome as a case study. *Front Hum Neurosci*. 2012;6:81. https://doi.org/10.3389/fnhum.2012.00081
83. Briegel W. Psychopathology and personality aspects of adults with Möbius sequence. *Clin Genet*. 2007;71(4):376-377. https://doi.org/10.1111/j.1399-0004.2007.00787.x

84. VanSwearingen JM, Cohn JF, Turnbull J, Mrzai T, Johnson P. Psychological distress: Linking impairment with disability in facial neuromotor disorders. *Otolaryngol Head Neck Surg*. 1998;118(6):790-796. https://doi.org/10.1016/S0194-5998(98)70270-0
85. Ha CY, Messieha ZS. Management of a patient with Möbius syndrome: A case report. *Spec Care Dentist*. 2003;23(3):111-116. https://doi.org/10.1111/j.1754-4505.2003.tb01671.x
86. Jacque D, Ossemann M, Timmermans J-M, Zdanowicz N, Dubois T. Mobius syndrome and obsessive compulsive disorder: A case report. *Psychiatr Danub*. 2019;31(SUPPL 3):376-380. https://pubmed.ncbi.nlm.nih.gov/31488755/
87. Hindawi. A new neurorehabilitative post-surgery intervention for facial palsy based on smile observation and hand-mouth motor synergies. n.d. https://www.hindawi.com/journals/np/2021/8890541/ (accessed September 20, 2022).
88. Moebius Syndrome - NORD (National Organization for Rare Disorders), NORD (National Organization for Rare Disorders). 2015. https://rarediseases.org/rare-diseases/moebius-syndrome/ (accessed September 20, 2022).
89. Lopez-Valverde G, Jarrin-Hernandez E, Cruz-Gonzalez F, Mateos-Sanchez E. Möbius syndrome: Surgical treatment for eyelid dysfunction. *COP*. 2013;4(3):229-233. https://doi.org/10.1159/000356528
90. Harrison DH. Surgical correction of unilateral and bilateral facial palsy. *Postgrad Med J*. 2005;81(959):562-567. https://doi.org/10.1136%2Fpgmj.2004.020321
91. Staples JW, Zuker RM, Borschel GH. Transfer of the deep temporal nerve for eyelid reconstruction in Mobius syndrome - an anatomic feasibility study and proposed surgical approach. *J Plast Reconstr Aesthet Surg*. 2022;75(1)265-270 https://doi.org/10.1016/j.bjps.2021.05.059
92. Magli A, Bonavolontà P, Forte R, Vassallo P. Lower eyelid surgery for lagophthalmos in Möbius and Poland-Möbius syndromes. *J Craniofac Surg*. 2011(6);e53-54. https://doi.org/10.1097/SCS.0b013e318231e22a
93. McKay VH, Touil LL, Jenkins D, Fattah AY. Managing the child with a diagnosis of Moebius syndrome: More than meets the eye. *Arch Dis Child*. 2016;101(9):843-846. https://doi.org/10.1136/archdischild-2015-310043
94. Ventura LO, da Cruz CB, de Almeida HC, Millar M, Lira AFC, Antunes DL. Seqüência de Möbius: Resultados a longo prazo, da correção cirúrgica do estrabismo. *Arq Bras Oftalmol*. 2007;70(2):195-199. https://doi.org/10.1590/S0004-27492007000200003
95. Lueder GT, Galli M. Long-term outcomes of strabismus surgery in Mobius sequence, *strabismus*. 2019;27(2):43-46. https://doi.org/10.1080/09273972.2019.1599402
96. Singh P, Vijayalakshmi P, Shetty S, Vora P, Kalwaniya S. Double augmented vertical Rectus transposition for large-angle esotropia due to sixth nerve palsy. *J Pediatr Ophthalmol Strabismus*. 2016;53(6):369-374. https://doi.org/10.3928/01913913-20160810-01
97. Rodrigues-Alves CA, Caldeira JAF. Moebius' syndrome: A case report with multiple congenital anomalies. *J Pediatric Ophthalmol Strabismus*. 1975;12(2):103-106. https://doi.org/10.3928/0191-3913-19750501-07
98. Sun LL, Gole GA. Augmented vertical rectus [corrected] transposition for the treatment of strabismus in Möbius syndrome. *J AAPOS*. 2011;15(6):590-592. https://doi.org/10.1016/j.jaapos.2011.07.012
99. Modi P, Arsiwalla T. Crocodile tears syndrome. In: *StatPearls [Internet]*. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK525953/
100. Sensat ML. Mobius syndrome: A dental hygiene case study and review of the literature. *Int J Dent Hyg*. 2003;1(1):62-67. https://doi.org/10.1034/j.1601-5037.2003.00010.x
101. Escoda-Francolí J, Sánchez-Garcés MA, Gay-Escoda C. Oral implant rehabilitation in a patient with Moebius syndrome. *Med Oral Patol Oral Cir Bucal*. 2009;1;14(6):E295-8. https://pubmed.ncbi.nlm.nih.gov/19300371/ (accessed September 20, 2022).
102. Terzis JK, Noah EM. Möbius and Möbius-like patients: Etiology, diagnosis, and treatment options. *Clin Plast Surg*. 2002;29(4):497-514. https://doi.org/10.1016/s0094-1298(02)00019-6