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Article: Comprehensive Review of Moebius Syndrome: Clinical Landscape, Etiology, and Therapeutic Challenges

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ABSTRACT

Moebius Syndrome, a rare congenital neuromuscular disorder, presents with non-progressive facial weakness, limited eye abduction, and diverse manifestations affecting cranial nerves. This comprehensive review explores its clinical landscape, emphasizing the need for extensive investigations into its elusive etiology and genetic underpinnings. The estimated prevalence is 1 in 250,000 live births, with sporadic cases prevailing. Initial symptoms, evident from birth, encompass difficulties in sucking, feeding, and absent facial expressiveness. Beyond musculocutaneous symptoms, diverse clinical manifestations extend to cardiac and psychiatric complications. Current research gaps, limited literature, and the absence of specific biological markers pose challenges in obtaining larger sample sizes for a more thorough understanding of the condition. The syndrome's impact on developmental milestones, cognitive function, and potential lifelong cognitive impairment necessitates a multidisciplinary approach. Surgical interventions, such as smile surgery and facial reanimation, offer corrective measures but face challenges in addressing severe congenital deformities. Lagophthalmos management, crucial for preventing complications, includes novel approaches utilizing the deep temporal nerve. Insights from ongoing genetic studies, a

cross-sectional investigation into the syndrome's natural history, and an exploration into language compromise contribute to advancing our knowledge. The paper underscores the urgency for continued research to develop standardized guidelines for diagnosis and management, addressing the existing gaps in understanding this complex syndrome. The current body of literature on Moebius syndrome is limited, and existing research highlights the imperative for more extensive investigations to unravel its elusive etiology, genetic underpinnings, and optimal management strategies. The absence of specific biological markers and the rarity of the condition contribute to challenges in obtaining larger sample sizes for research.

Keywords: Moebius Syndrome, Neuromuscular disorder, MRI, Computational methods, Data analysis, Modeling molecular interactions

ABBREVIATIONS

OMIM – Online Mendelian Inheritance in Man

ICSI – Intracytoplasmic Sperm Injection

EMG – Electromyography

NCS – Nerve Conduction study

MRI – Magnetic resonance imaging

EEG – Electroencephalogram

CCDD – Congenital Cranial Dysinnervation Disorder

INTRODUCTION

Moebius syndrome, a rare congenital neuromuscular disorder, is characterized by non-progressive facial weakness and restricted eye abduction. Individuals afflicted by this syndrome commonly experience challenges in activities such as smiling, mouth closure, and chewing. Beyond facial nerve involvement, Moebius Syndrome can impact other cranial nerves, albeit with varying frequencies [1]. The condition was initially documented by Von Graefe in 1880 and further detailed by Moebius in 1888. The estimated prevalence of Moebius syndrome is 1 in 250,000 live births, with an equal distribution among males and

females. Although the majority of cases are sporadic, familial instances account for approximately 2% [2].

The primary symptom, apparent from birth, is the inability to suckle. Additional indications encompass difficulties related to feeding, swallowing, and choking, coupled with the absence of facial expressiveness, strabismus, motor developmental delays, and challenges in hearing and speech. Anomalies affecting the tongue, jaw, and limbs, including conditions such as clubfoot and anomalies in finger structure, may also be present [3]. Over time, the clinical manifestations have expanded to include not only musculocutaneous symptoms but also cardiac and psychiatric complications [4][5].

Despite being initially elucidated by Von Graefe and Moebius, the cause and pathogenesis of Moebius syndrome remain elusive and contentious. Although the etiology remains uncertain, theories linking Moebius Syndrome to embryological subclavian artery disruptions and various genetic and environmental factors have been proposed [6][7]. Associations with other syndromes, such as Poland syndrome, Pierre Robin sequence, Carey-Fineman-Ziter syndrome, and Klippel-Feil anomaly, have also been reported [8]. Alternative designations for the syndrome include congenital facial diplegia, nuclear agenesis, congenital nuclear hypoplasia, congenital oculofacial paralysis, and congenital abducens-facial paralysis. Significant overlap with syndromes like hypoglossia-hypodactyly syndrome, Charlie-M syndrome, and glossopalatine-ankylosis syndrome has been observed [9].

This study acknowledges certain limitations that warrant careful consideration. The retrospective design and the relatively small patient cohort may restrict the generalizability of the findings. Due to the rarity of Moebius syndrome, acquiring larger sample sizes poses a considerable challenge. Additionally, the absence of specific biological or genetic markers for Moebius syndrome introduces the potential for confusion with other neurological disorders or congenital malformation syndromes. The scarcity of comprehensive literature on Moebius syndrome and its associated features underscores the existing research gap, emphasizing the need for more extensive investigations to enhance our understanding of this uncommon condition.

ETIOLOGY AND GENETICS

The precise etiology of Moebius syndrome remains elusive, with current hypotheses suggesting a combination of genetic factors, notably de novo mutations, and ischemic insults during embryogenesis. Genetic testing is pivotal for diagnosis, though the specific genetic mutations associated with the syndrome are not fully elucidated, necessitating further research to comprehensively understand its genetic basis. It is crucial to acknowledge the study's limitation in terms of a relatively small patient cohort, precluding definitive conclusions on causality or the emergence of new symptomatology [1][5].

Determining the exact cause of Moebius syndrome is challenging due to its diverse presentations. A study investigating genetic factors identified allelic defects in the REV3L and PLXND1 genes, suggesting their involvement in a substantial portion of cases [10]. Genetic loci at 3q21-q22 and 10q, designated as number 15700 on Online Mendelian Inheritance in Man (OMIM) with a gene map locus at 13q12.2-q13, have been associated with the syndrome [11]. The homeobox gene family, particularly HOXA1, HOXB1, and SOX14, along with mutations in the TUBB3 gene, have been implicated in Moebius syndrome pathogenesis [12-15].

Researchers propose that the syndrome's varied defects point to an embryological origin, with suspected ischemic damage affecting the vertebral-basilar system and second pharyngeal arch. Hemorrhage, stenosis, or thrombosis in facial arteries and second pharyngeal arch veins may cause ischemia, leading to underdeveloped cranial nerves—a major cause of the syndrome. Disruptions in the blood flow to developing subclavian arteries may lead to anomalies such as the absence of the pectoralis major and limb abnormalities. This could be attributed to episodes of hypothermia and hypoxia during embryonic development. [6][1].

Moreover, evidence suggests a connection between vascular insults and prenatal exposure to teratogens like cocaine, alcohol and ergotamine [1]. This association gains support from findings linking teratogenesis and abortifacients to a higher incidence of Moebius Syndrome. Thalidomide's teratogenic effects disrupt cranial nuclei in the brain stem, leading to cranial nerve VI and VII hypoplasia—a significant factor in Moebius Syndrome [16]. Research consistently provides strong evidence supporting a significant association between the use of misoprostol and the occurrence of Moebius Syndrome [7][17][18][19]. Notably, affected structures typically originate between the 3rd and 7th week of embryonic life, aligning with the period of highest vulnerability to teratogenic influences, reinforcing the embryologic origin of Moebius Syndrome [1].

Any occurrence disrupting circulation between the uterus and the fetus, such as trauma, membrane rupture, pharmacological impacts, hyperthermia, or unspecified factors, could play a role in Moebius syndrome development. Recording events during pregnancy and exploring the fetal brainstem in animal models are recommended for deeper insights. Potential alcohol abuse during the first trimester has been linked to limb deficiencies and cranial nerve palsies. Alcohol abuse can induce spasms in the umbilical artery or other fetal vessels, resulting in hypoxic-ischemic insults. Rodent models have demonstrated a higher occurrence of limb deficiencies and syndactyly due to alcohol exposure during organogenesis [20].

Additionally, rare cases suggest a potential connection between the use of artificial reproductive technologies like intracytoplasmic sperm injection (ICSI) and in-vitro fertilization (IVF) with Moebius Syndrome occurrence [21]. However, due to the lack of conclusive evidence, the exact etiology of Moebius Syndrome remains uncertain.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical researchers and medical professionals have extensively documented the evolving clinical presentations of Moebius Syndrome over the years. The classical clinical phenotype, characterized by paralysis of cranial nerve VII (96%) and cranial nerve VI (85%), has gradually revealed a spectrum of manifestations, encompassing total, partial, unilateral, or bilateral occurrences.

Clinical presentations involve challenges in effective sucking, absence of facial mimicking, fixed gaze, incomplete eyelid closure during sleep, ptosis, hypotonia, and developmental delays. Ocular motility alterations may manifest as orthotropia with a complete lack of ocular movements, substantial esotropia (convergent strabismus), or significant exotropia (divergent strabismus), often accompanied by torticollis [2]. Compound hyperopic astigmatism is the most frequently observed refractive error [22]. Lacrimation onset is typically delayed, occurring between 4 to 6 months, with subsequent experiences of the crocodile tear phenomenon, dry eyes, and epiphora [23][24][25]. Commonly observed conditions include bilateral epicanthus, unilateral amblyopia, stereopsis issues, abnormal binocular vision, suppressive scotoma, and photophobia. Notably, in cases of lagophthalmos, corneal damage is typically absent, thanks to the preserved Bell's phenomenon [4][23].

Developmental challenges encompass broad delays in global developmental, motor, emotional, and speech domains, as well as deficiencies in hand-eye coordination. It is noteworthy that most children with Moebius syndrome exhibit a normal developmental

quotient, with only a small percentage experiencing cognitive deficits [2]. Bilateral facial nerve paresis of central or peripheral type is observed in 90% of cases, with hypoglossal nerve paresis occurring in 50% of cases. Brachial malformations in the upper extremities, including congenital amputation, brachydactyly, syndactyly, and clubhand/clubfoot, are common. Rarely, cognitive impairments, including autism and mental retardation, may be present [26]. Familial Moebius Syndrome cases often exhibit no musculoskeletal involvement, with a transmission risk of approximately 2% [2][27].

Orthodontic issues such as lip and palatal clefts, malocclusion with micrognathia, reduced temporomandibular movements, and excessive maxillary development are observed in patients with Moebius Syndrome [28]. Other orthodontic problems may include microstomia, high-arched palate, tongue malformation, bifid uvula, cleft lip or palate, and dental malocclusion [29]. The syndrome is marked by a general developmental lag at the age of one, exhibiting compromised speech, motor skills, and emotional maturity by the age of two, which tends to normalize by the age of three. Certain individuals may encounter challenges in cognitive abilities, hand-eye coordination, and maintain an average IQ until the age of five, with a 10% likelihood of enduring lifelong cognitive impairment. [1].

Current investigations are focusing on potential causative genetic patterns in the diagnosis of Moebius Syndrome [10]. Table 1 below represents the different kinds of symptoms and conditions in moebius syndrome and their respective diagnostic methods. Diagnostic methodologies, including electromyography (EMG), nerve conduction studies (NCS), ultrasonography, and magnetic resonance imaging (MRI), have become integral in the diagnostic process. EMG and NCS are highly effective in diagnosing and distinguishing Moebius Syndrome from other causes of congenital facial weakness with neuropathic and myopathic origins [30]. Regarding imaging techniques, MRI stands out for its exceptional ability to visualize abnormalities in cranial nerves and associated structures, with the bilateral absence of facial and abducens nerves emerging as a distinctive MRI feature in the context of Moebius Syndrome [31].

Table 1: Represents the different kinds of symptoms and conditions in moebius syndrome and their respective diagnostic methods.

CONDITIONS	DIAGNOSIS

Cerebral palsy	MRI, electroencephalogram (EEG), CT scan and genetic testing [32].
Facial nerve dysfunction	Electromyography and nerve conduction test [33][34].
Metabolic myopathy	Electromyography, muscle tissue biopsy and blood test for markers [35].
Facial palsy from trauma	Nerve conduction test [36][37].
Duane Syndrome	Clinical diagnosis by the age of 10. Patients lack facial nerve palsy features [38].
DiGeorge Syndrome	Clinical features with symptoms like cardiac anomalies, hypoparathyroidism, an underdeveloped lower jaw, narrow nasal passages [39].
Hanhart Syndrome	Physical features like peromelia, hypoglossia, micrognathia and hypodactylia [40].
Charlie M Syndrome / claw hand deformity	Physical features like large set ears, broad nose and microcephaly [41].
Klippel Feil anomaly	Clinical examination and imaging studies based on symptoms like two or more spinal bones in neck, torticollis, low hairline and short neck [42].

FACIAL PARALYSIS

In 96% of Moebius syndrome cases, individuals encounter facial paralysis, leading to the absence of facial expressions, an inability to smile, and the incapacity to mimic facial movements. The resultant facial paralysis in Moebius syndrome contributes to challenges in neonatal sucking and difficulties in closing the eyelids during sleep, resulting in incomplete closure and ptosis. Beyond the physical ramifications, facial paralysis can significantly impact social development, self-perception, and communication with peers throughout childhood and adolescence [2].

The paralysis of the VI and VII cranial nerves in Moebius syndrome induces the loss of muscle function they innervate, resulting in the absence of lateral gaze and facial animation. Bilateral paralysis may manifest asymmetrically, primarily affecting the lower face with

limited platysmal or depressor anguli oris activity. Crucial facial movements, such as lower-lip support, upper-lip elevation for smiling, and commissure movement, are absent, contributing to the misconception of dullness or disinterest due to the inability to smile. Speech difficulties arise, characterized by flaccid dysarthria marked by challenges in bilabial sounds. Eating and drinking issues emerge, including food pocketing, dribbling, and severe drooling, stemming from lower face paralysis [43,8].

Given the significant role of the face in social interactions, challenges in social interactions are frequently observed in individuals with Moebius syndrome, particularly during developmental stages. This may serve as a risk factor contributing to later social and psychological difficulties in adulthood. To improve the quality of life and address speech and oral competence, numerous intervention programs have been suggested. These interventions encompass strategies such as neuromuscular training, meditation-relaxation, respiratory control, massage, as well as psychological and communication approaches [44].

ASSOCIATED ANOMALIES

The paralysis of the sixth cranial nerve in Moebius syndrome results in the inability to laterally move the eye, a commonly associated anomaly that tends to occur bilaterally and completely. Occasionally, the oculomotor and trigeminal nerves may also be impacted. While horizontal eye movement is paralyzed, vertical movement remains unaffected, and there may be some degree of convergence present. Limb malformations are frequently observed in Moebius syndrome, with clubfoot being the most prevalent, affecting about one-third of cases either bilaterally or unilaterally. Digital anomalies, such as syndactyly or brachydactyly, are commonly present. Ectrodactyly (split hand) and terminal transverse defects may also occur. Additional anomalies include stiffness of the index fingers, marked bilateral valgus deformity of the distal phalanges of the big toes, and, less commonly, arthrogryposis multiplex congenita, Klippel-Feil anomaly, and dextrocardia. Craniofacial abnormalities involve external ear defects, small palpebral fissures, hypertelorism, micrognathia, epicanthic folds, and microstomia [9].

Characteristic orofacial anomalies in Moebius syndrome include tongue fasciculations, mandibular hypoplasia, and difficulties in pronunciation. Rarely, there may be associated organ defects such as genitourinary abnormalities, congenital heart disease, and hypogenitalism [45].

CRANIAL NERVE ABNORMALITIES

A spectrum of extracranial manifestations has been observed in conjunction with Moebius Syndrome, as evidenced by various studies. In a study conducted by Bosch-Banyeras, an abnormal male with cranial nerve impairment (VI, VII, IX, and X) exhibited Dextrocardia in Poland Syndrome – Moebius Syndrome [46]. Another study by Thapa documented a 2-year-old male with cranial nerves VI and VII involvement presenting Atrial-Septal Defect. Clinical features included a Grade III/VI ejection systolic murmur, a fixed split-second heart sound, and a 6 mm ostium secundum defect visualized through CT scan [47].

Hashimoto reported a 17-year-old male with cranial nerves II, VI, VII, and VIII involvement showcasing Pituitary dwarfism and Hypoplastic Optic Disc. Clinical findings included highly retarded bone growth, small-sized thyroid and pituitary glands and infantile external genitalia [48]. Kawai examined a 15-year-old male with cranial nerves II, III, VI, and VII involvement, revealing Hypogonadotropic hypogonadism and peripheral neuropathy. Manifestations included the absence of secondary sexual characteristics, hypogonadism, and lower motor neuron lesions [49]. Ichiyama reported a 19-year-old female with cranial nerve involvement (III, VI, VII) presenting with Premature thelarche, marked by early breast development at ten months [50].

Tanaka documented a case of neurogenic bladder in an individual with cranial nerve involvement (VI, VII), noting urinary retention since birth and evolving complications such as irregular bladder walls and detrusor overactivity over time [51]. Other studies by John, Buccoliero, Freire, Viteri, Preis, and Chen explored diverse manifestations, including Dandy-Walker variant, splenogonadal fusion, Ankyloglossia Superior syndrome, Goldenhar anomaly, and early eruption of deciduous teeth, respectively [52][53][54][55][56][29]. These instances underscore the varied extracranial manifestations associated with Moebius Syndrome across different cranial nerve involvements. Figure 1 shows overview of moebius syndrome.

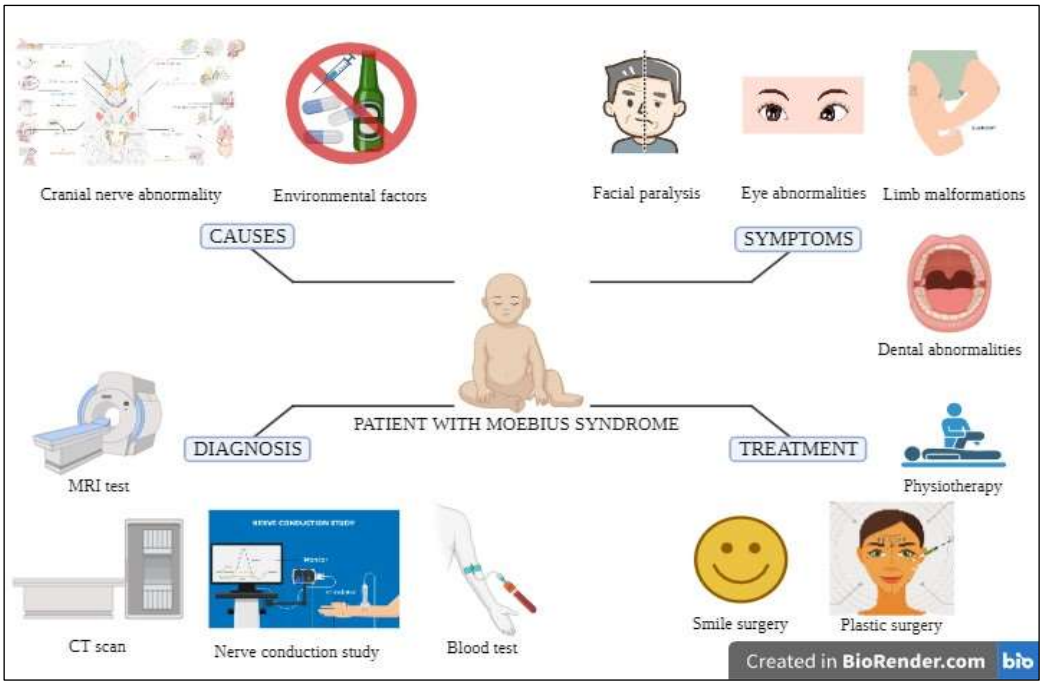

Figure 1: Illustrates the causes, symptoms, diagnosis and treatment of moebius syndrome.

MEDICAL MANAGEMENT AND TREATMENT

The diagnosis of Moebius Syndrome relies on clinical assessment, and distinct radiological features are identifiable in imaging studies. While there is no absolute cure for Moebius Syndrome, a multidisciplinary strategy is utilized to offer supportive care and address both physical and psychological challenges. Treatment primarily targets the enhancement of skeletal alignment, facial aesthetics, and oral issues. Utilizing combined orthopedic-orthodontic therapy, orthodontic camouflage has been employed to improve skeletal misalignment and enhance facial appearance [57]. Dental care for individuals with Moebius Syndrome is critical for overall well-being, and a multidisciplinary healthcare team is essential for maintaining oral hygiene and dental health [17]. Management strategies involve supportive and symptomatic approaches, incorporating physiotherapy and consultations with orthopedics. Psychological support and smile rehabilitation, often involving collaboration with a plastic surgeon, are also integral components of the management plan [29]. Moebius Syndrome can lead to serious complications such as severe dysphagia and aspiration pneumonia, posing potential life-threatening risks. As a precaution, individuals at heightened risk are advised to follow a specific diet. Furthermore, in situations where there is a compromise in airway function, opting for an elective tracheostomy might be beneficial,

ensuring easier breathing and effective airway clearance [58]. There is a need for the development of standardized guidelines for the medical management and treatment of Moebius Syndrome.

Restoring even minimal voluntary facial movements can significantly enhance both verbal and non-verbal communication, addressing various daily challenges such as eating, drinking, and facial expressions. The treatment of facial muscle atrophy or aplasia commonly involves "Smile surgery," where a segment of the gracilis muscle from the leg is transplanted. The muscle segment which is transplanted receives innervation from unaffected parts of the facial nerve, ensuring functionality. Vascularization of the graft is achieved through anastomoses between facial vessels and the Vena comitans of the Gracilis [43]. While preserving facial aesthetics is crucial during the procedure, outcomes may vary, with the first contractions typically observed three to six months post-surgery. Additional months of physiotherapy and neurorehabilitation follow before achieving a smile. However, asymmetry may persist, attributed to the trigeminal nerve's involvement in facial sensory and motor functions [44]. Other approaches employed in facial reanimation surgery include the transfer of the temporalis tendon and bilateral selective neurolysis [59].

Moebius syndrome presents abnormal ocular mobility, including strabismus, conjugate gaze palsies, and Duane’s retraction syndrome. Incomplete eyelid closure can lead to corneal issues and potential blindness due to the imbalance between orbicularis oculi and levator palpebrae superioris functions. Early ophthalmological evaluation is crucial to prevent corneal problems and address gaze palsies. Surgical interventions like botulinum toxin injections into the medial rectus muscle can prevent contractures but also aid in subsequent strabismus correction surgery [60]. Various surgical interventions are accessible for diverse strabismus patterns, encompassing medial rectus recessions, combined recessions of the medial rectus muscle, resection of the lateral rectus muscle, and transposition of vertical and/or inferior rectus muscles [61][62]. Numerous studies have demonstrated successful outcomes and enhanced abduction function following these procedures [63][64].

Lagophthalmos poses risks of keratitis, dry eyes and other drastic complications like corneal ulceration or perforation. Mild cases are typically controlled with lubricants and hygiene methods, while severe or refractory cases may necessitate surgical intervention [65]. A common procedure involves an implantation of gold-weight in the upper eyelid, often combined with muscle grafts like the platysma muscle for lasting relief [66][65].

Tarsorrhaphy is preferred for lower eyelid dysfunction, and alternative methods encompass muscle or fat transfers and fascia slings [66]. Recently, researchers have suggested a novel approach involving the use of the deep temporal nerve for muscle graft transfer and demonstrating a successful continual handling of lagophthalmos through blepharoplasty with various grafts [67][68].

Early rehabilitation, coupled with parental assistance, plays a pivotal role in enhancing the long-term physical and psychological prognosis of children affected by Moebius syndrome [2]. The existence of social stigma towards visible signs of neurological disorders, resulting in insufficient support, particularly from parents, can have profound implications on the psychological well-being of these children [69]. Surgical interventions offer corrective measures for orofacial and limb deformities, contributing to improved rehabilitation outcomes. Infants, often faced with orofacial abnormalities, may require feeding assistance and nutritional management. Rehabilitation encompasses crucial elements such as physical, occupational, and speech therapy. Additionally, recent advancements in management involve innovative surgical techniques like temporalis tendon transfer and bilateral selective neurolysis [59].

Addressing the comprehensive array of defects associated with Moebius Syndrome through surgery presents considerable challenges. Successful treatment demands a thorough reliance on clinical and electrophysiological evaluations to understand the extent of dysfunction in major structures and identify the underlying causes, particularly the loss of innervation. While surgical interventions may offer benefits, they may not be curative or substantially impactful for severe congenital deformities. More conservative treatment approaches can play a role in helping patients adapt to their lifestyle. In some instances, plastic surgery may be considered contingent upon the patient's preferences and choices.

CLINICAL TRAILS

This cross-sectional study provides a comprehensive exploration into the natural history of Moebius syndrome (MIM 157900), a complex developmental disorder characterized by congenital facial weakness, limited eye abduction, and associated anomalies. Employing a multi-faceted approach encompassing clinical, molecular, and imaging methodologies, the research utilizes whole exome sequencing and brain imaging studies to delineate the clinical phenotype, identify disease-causing genes, and unravel the molecular pathways involved. The

study, inclusive of a diverse population aged 2 to 80 recruited through the Moebius Syndrome Foundation, aims to assess outcomes through comprehensive clinical evaluations, neurocognitive screenings, electromyography, and genetic and imaging analyses, providing valuable insights into Moebius syndrome and related conditions [70].

Möbius syndrome, influenced by genetic and environmental factors, manifests as facial and abducens nerve lesions with limb malformations. Conducted from February to December 2002 at a genetic diagnosis center in Ceará, this study characterizes oral language in fifteen subjects aged 2 to 13 with Möbius syndrome. Findings reveal variable language compromises across morphology, syntax, semantics, and pragmatics, with consistent challenges in linguistic development, speech comprehension, and sentence construction. The study underscores the importance of gaining a deeper understanding of language compromise in Möbius syndrome [71].

The Engle Lab's decade-long investigation into the genetics of strabismus and eyelid movement disorders has expanded to include Congenital Cranial Dysinnervation Disorders (CCDDs). Genetic studies on individuals with eye movement disorders reveal additional ocular defects, vascular issues, limb abnormalities, and more. The study contemplates enrolling individuals without eye defects but with symptoms linked to CCDD gene mutations, with the aim of comprehensively understanding the spectrum of investigated disorders [72].

This pilot study delves into the effectiveness of Positive Exposure's intervention for individuals with craniofacial differences, utilizing professional photo-shoots and video interviews. Drawing on the positive experiences of individuals with conditions like albinism and Marfan syndrome, the study integrates qualitative and quantitative measures to understand perceptions of being photographed and filmed. While not statistically powered, the pilot study provides foundational insights for future research on the intervention's efficacy in larger populations with genetic differences [73].

CONCLUSION

In conclusion, Moebius syndrome, marked by non-progressive facial weakness and limited eye abduction, presents a complex clinical profile with diverse manifestations and associated challenges. Despite its rarity, the syndrome warrants attention due to its profound impact on

various aspects of patients' lives. The comprehensive array of defects associated with Moebius syndrome underscores the need for a thorough understanding of the extent of dysfunction in major structures and the underlying causes, particularly the loss of innervation. While surgical interventions offer corrective measures, particularly in addressing facial paralysis, their curative impact on severe congenital deformities remains a challenge. The existing gaps in literature emphasize the urgency of further research to enhance our understanding of this rare condition and to pave the way for more effective and standardized guidelines for diagnosis and management.

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AUTHORS CONTRIBUTION

All the authors have equally contributed to the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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