Moebius syndrome: A review of literature
Tejavathi Nagaraj, Soniya Kongbrailatpam, Sushant Anant Pai, Pathik Debnath, Priyanka Ramasamy, Shamama Mumtaz
Department of Oral Medicine and Radiology, Sri Rajiv Gandhi College of Dental Science and Hospital, Cholanagar, Bengaluru, Karnataka, India

Abstract
Moebius syndrome is a congenital neurological disorder, which frequently shows facial diplegia with bilateral lateral rectus palsy, but there are variations. The definition and diagnostic criteria for Moebius syndrome vary among authors, it is defined as congenital facial weakness with abnormal ocular abduction. Deformities such as muscular dystrophies and mental retardation have also been associated with this syndrome. The list of signs and symptoms mentioned in various sources for Moebius syndrome includes more than 20 peculiar features. This review of literature includes classification and grading system of Moebius syndrome, their features, etiology, and management.

Keywords:
Cranial nerves, facial palsy, Moebius syndrome, oral health

Introduction
Moebius syndrome is a neurological disease, non-progressive congenitally occurs unilaterally or bilaterally weakness or palsy of more than 2 cranial nerves, mostly the abducens and facial nerves. Third and twelfth cranial nerves are also frequently involved. This type of syndrome was reported by Von Graefe in 1880 and Moebius in 1888. Prevalence is approximately 1/200,000 in live birth populations and equally distributed in male and female.

An International Group of Experts in 2007 prepared a criterion about how to diagnose Moebius syndrome. They are as follows: First, congenital facial paralysis affecting of both sides or complete paralysis of one limb, they affect lower efferent neuron of the peripheral nervous system, and second, unable to move lateral movements of the eyeball and abnormal alignment of the eyes because of abducens nerve paralysis.

The syndrome may also include cranial nerves such as III, V, VIII, XI, and XII with other abnormalities such as tongue fasciculations, cleft palate, and mandibular hypoplasia; skeletal abnormalities such as fusion of one or more digits, shortening of fingers and toes, abnormal curve of spine, curving of joints, absence of pectoral muscles, delayed puberty, impaired sense of smell, lack of production of certain hormones, and Carey–Fineman–Ziter syndrome which id combined with Moebius syndrome and Pierre Robin syndrome, and skin abnormalities such as macules and axillary web syndrome. Some patients reported autism and poor connection with society around 30–40% according to Ana et al. due to loss of facial expression. Figures of Moebius syndrome of a girl is given from Figure 1-3.

Classification and Grading System
The first district, “C” as cranial nerve, is divided into three groups based on severity of paralysis

- **Group A:** Bilateral complete paralysis of abducens and facial nerves (Moebius syndrome).
- **Group B:** Paralysis of abducens and facial nerves with residual function of some nerve muscle units of the face unilaterally (incomplete Moebius syndrome).
- **Group C:** Unilateral facial paralysis (Moebius-like syndrome).

Towfighi et al. classified Moebius syndrome into four categories according to alterations in their pathology

Category A includes underdevelopment of cranial nerve nuclei and presumably as.
Category B includes the main lesions of the surrounding cranial nerves.

Category C comprises focal necrosis in brainstem nuclei indicates fetal infection and blood loss and shock due to less oxygen supply of the mother during gestation period.

Category D includes no lesions in the CNS or having disease of the muscle.

Some pathogenesis are investigated, and suggestive causative factors are intrauterine vascular, toxic, genetic, and infections.

The etiopathogenesis of Moebius syndrome remain unknown and still discuss, if it is caused genetically. The suggested etiological factors include lack of motor nuclei of the VI and VII cranial nerves, loss of function, and organs such as hypoxic–ischemic encephalopathy, brain injury (caused by

Table 1: Of Moebius syndrome: Authors’ findings and management

| Authors                  | Findings                                                                 | Management                                                                 |
|--------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 1. Srinivas et al. 2016  | Magnetic resonance imaging brain of a 2-year-old girl showed the following findings:  
- Absent of cisternal and canalicular segments of left facial nerve  
- No visualization of cisternal segments of bilateral abducens nerves  
- Flattened floor of fourth ventricle with absence of bilateral facial colliculi | Since the disease is congenital and non-progressive, no definitive and established treatment has been described |
| 2. John and Vanitha 2013 | The magnetic resonance imaging of a 15-month-old male child showed complete agenesis of the corpus callosum with inferior vermis hypoplasia with prominent fourth ventricle which is consistent with the Dandy-Walker variant (includes vermin hypoplasia and cystic dilation of the 4th ventricle without enlargement of the posterior fossa) | Since the disease is congenital and non-progressive, no definitive and established treatment has been described. |
| 3. Kulkarni et al. 2011  | A case of 18-year-old male showed the theory of nuclear hypoplasia that appears to hold good for III, VI, and VII nerve involvement and the gaze palsy, but the associated features like maldevelopment of foot and palm with webbing of fingers showed that the diverse manifestations of Moebius sequence are due to some noxious agents acting on the embryo at the time of development | Since the disease is congenital and non-progressive, no definitive and established treatment has been described. |
| 4. Slee et al. 1991      | A case of a 2½-year-old female showed classical features of Moebius syndrome in association with a deletion of chromosome 13 (46, XX, del (13) (q12.2) | Since the disease is congenital and non-progressive, no definitive and established treatment has been described |
| 5. Harbord et al. 1989   | A case of male infant which is associated with unilateral cerebellar hypoplasia is unusual but consistent with a vascular disruption occurring in the basilar artery early in its development | Since the disease is congenital and non-progressive, no definitive and established treatment has been described |
| 6. Futman et al. 1973    | A case of a 32-year-old male showed loss of function of the abductors of the eye and paresis of the muscles of the lower portion of the face and the tongue. The underdeveloped mandible could possibly have resulted from that paresis. Except for slight arthritic changes in both legs, other anomalies of the extremities or trunk were not present (Henderson, 1939) | Surgical treatment such as Obwegeser sagittal osteotomy of maniple and chin reposition and rhinoplasty was done |
| 7. Gadoth et al. 1979    | A case of a 6-year-old boy evaluated for congenital strabismus. This review showed that the use of thalidomide in early pregnancy associated with non-progressive facial, extraocular, lingual, and pectoral muscle agenesis, together with the skeletal deformity of symbrachydactyly represents the result of an intrauterine mesodermal defect impairing the development of these structures | Since the disease is congenital and non-progressive, no definitive and established treatment has been described |
| 8. Di Blasio et al. 2013 | In the Moebius patients, the constant limitation of temporomandibular joint movement during growth seems to lead to the permanent limitation in the articular movement range. It is well known that the Moebius syndrome affects mimic muscles activity when muscles related to mandibular opening, protrusive and lateral movements are not directly damaged | These observations suggest the importance of an adequate functional rehabilitation program, starting from an early age, to improve temporomandibular joint movements |
| 9. Kuhn et al. 1990      | A case of newly born boy to a 17-year-old woman showed that brainstem calcification on computed tomography confined to the abducens nuclei was strongly suggestive of Group III Moebius syndrome | Since the disease is congenital and non-progressive, no definitive and established treatment has been described |

(Contd...)
| Authors                                      | Findings                                                                                                                                                                                                 | Management                                                                                     |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 10. Ha and Messiah in 2003[21]              | A case of an 18-year-old Hispanic male reported with a chief complaint of teeth hurt                                                                                                                     | Surgical correction of facial paresis was done. Surgical treatment for the relief of bilateral facial paralysis has been attempted using the temporalis muscle for transplantation or using platysma muscle. Bilateral transfer of the anterior third of the masseter muscles to the corners of the mouth also has been attempted |
| 11. Elsahy in 1973[22]                      | Due to taking of thalidomide during miscarriages and throughout the last pregnancy, a 1-year-old girl showed mask like facies, more apparent during crying. All facial movements were absent, unable to close eyelids completely, no conjugate movements of the eyes to either side could be detected; however, vertical elevation and depression were infrequently noted. The mouth was always open and the corners drooped, shrunken tongue, unable to protrude beyond her teeth, atrophic papillae. Right hand smaller than the left, syndactylysis | 1. A Denis Browne splint was used to correct the tibial torsion and the inversion of the feet  
2. In November 1967, an operation on the right hand was done to correct the syndactylysis  
3. In May 1968, a bilateral temporalis transfer to the lips was performed |
| 12. Budic et al. in 2016[23]                | A case of a 10-year-old girl with Moebius syndrome was scheduled for multiple tooth extraction surgery. Characteristic clinical expressions such as mask-like facies, strabismus, severe hypotonia, microglossia, micrognathia, high palate, limited mouth opening, inadequate coughing and swallowing reflexes, and respiratory problems due to frequent aspirations, nasal ulceration, crescent-shaped ulceration at the right corner of the mouth, trophic changes of the skin bilaterally along the third division of the trigeminal cranial nerve, hypoplastic corpus callosum, ventriculomegaly, developmental delay, limb anomalies (clubfoot), and hypoplastic right pectoral muscle | Due to the diverse spectrum of clinical findings in patients with Moebius syndrome, standard anesthetic plan for these patients cannot be made in advance. Based on our experience, only careful pre-operative evaluation, along with meticulous physical examination can identify the specific end-organ involvement and thereby allow the most optimal plan for airway management in a patient with Moebius syndrome |
| 13. Krajcirik et al. in 1985[24]            | A case of a 13-year-old girl with Moebius syndrome and recurrent pulmonary aspiration was scheduled for diagnostic fiber-optic bronchoscopy because of persistent left lower lobe pneumonia. Previous examination revealed expressionless facies, marked bilateral facial paralysis, and dysarthria, could not gaze fully to right or left, gag reflex was present, but poor elevation of uvula, bilaterally impaired corneal reflex | Moebius syndrome and repeated episodes of aspiration and pulmonary complications tolerated well nitrous oxide-fentanyl anesthesia with a d-tubocurarine-pancuronium mixture, during fiber-optic bronchoscopy. However, after the bronchoscopy, the patient developed acute respiratory failure due to excessive secretions in the airway and required tracheal intubation and respiratory support for 48 h. We recommend that these patients be medicated preoperatively with an antisialagogue and receive intensive respiratory support postoperatively, preferably with the tracheal tube in place, to facilitate bronchial toilet |
| 14. Mussi et al. in 2016[25]                | The study included 30 subjects, MS group (n=15) and the healthy control group (CG, n=15). The salivary flow rate was measured from unstimulated and stimulated whole saliva and bilateral PS by calculating milliliters of saliva per minute. The right and left paraffin stimulation was evaluated separately | The salivary changes found in MS subjects, as the reduced salivary flow, increased amylase activity and a lower buffering capacity, may be related to higher incipient carious lesions in MS group. These results provide novel information regarding the dental caries increased risk on individual with MS |
oxygen deprivation to the brain, which occurs in between 5 and 6 weeks of gestation period), diseases of the blood vessels, gastrointestinal tract infections, exposure to drugs (thalidomide or misoprostol), alcohol, cocaine, and a genetic component such as remodeling of PLXND1 and REV3L genes. It is already reputed that a major problem show an occurrence of damage of brainstem in one or more particular areas where the phase of embryogenesis occurs. Oral manifestation includes thin or small upper lip, congenital or acquired reduction in the size of the oral aperture, hanging corner of the mouth, micrognathia, high arch palate, weakness of tongue, grooves in tongue, loss of tongue papilla, and inability to close mouth.

Magda et al. in 1999 found a 14-month-old baby boy diagnosed as Moebius syndrome due to misoprostol taken in the 8th week of intrauterine life which includes disorder manifesting as sleep-associated alveolar hypoventilation, which mostly seen

| Table 1: (Continued) |
|-------------------|-----------------|-----------------|
| Authors           | Findings                                    | Management                                    |
| 15. Julia et al. in 2010[26] | A data collection was performed by retrospective review on six patients with Moebius syndrome who underwent direct tongue neurotization. Each patient was videotaped for 30 min preoperatively and postoperatively according to a standardized protocol | Result showed considerable improvement in speech intelligibility and articulation. Higher improvement was noted in patients with partial bilateral hypoglossal involvement than in patients with complete unilateral involvement of the hypoglossal nerve, as well as in younger patients. Tongue neurotization has therefore an important role in restoring the ability of these patients to communicate and obtain the potential to develop normal social skills. |
| 16. Fernandes et al. in 2013[27] | A case of a 7-month-old boy, first twin, weighing 6.5 kg presented with Moebius syndrome was admitted for clubfoot repair. The patient had malignant hyperthermia after exposure to sevoflurane and succinylcholine, which was readily reversed with dantrolene maintained for 24 h. Ten hours after dantrolene discontinuation, there was recrudescence of malignant hyperthermia that did not respond satisfactorily to treatment, and the patient died. | Musculoskeletal disorders in children are associated with increased risk of developing malignant hyperthermia, although Moebius syndrome has not yet been reported. Dantrolene is the drug of choice for treating this syndrome; prophylaxis is indicated during the first 24–48 h of the episode onset. The main risk factors for recurrence are muscular type, long latency after anesthetic exposure, and increased temperature. The child had only one risk factor. This case leads us to reflect on how we must be attentive to children with musculoskeletal disease and maintain treatment for 48 h. |

Figure 1: Facial profile

Figure 2: Unable to close eyelids (lagophthalmos)
Moebius syndrome: Review of Literature

Nagaraj, et al.

Towfighi J, Marks K, Palmer E, Vannucci R. Moebius syndrome. Neuropathologic observations. Acta Neuropathol 1979;48:11-7.

Figure 3: Tongue fasciculations

in the early stage after birth. Symptoms may include bluish discoloration of the skin due to inadequate oxygen supply of the blood, cessation of breathing, respiratory arrest, and congenital central hypoventilation syndrome.12) Many authors had given findings and management of Moebius syndrome in Table 1.

Conclusion

It is important to diagnosis and rehabilitate to get proper information. It is also necessary to counsel both the child and parent about this syndrome. For management, this type of patient needs multidisciplinary approach which involves qualified trainers to perform different types of therapies. And at last, we should analyze large number of populations and need more investigation to find out the etiology and complications of this type of syndrome.

References

1. Picciolini O, Porro M, Cattaneo E, Castelletti S, Masera G, Mosca F, et al. Moebius syndrome: Clinical features, diagnosis, management and early intervention. Ital J Pediatr 2016;42:1-13.
2. Miller G. Neurological disorders. The mystery of the missing smile. Science 2007;316:826-7.
3. Chowdhury S, Sarkar S, Guha D, Dasgupta MK. Case report-moebius syndrome: A rare entity or a missed diagnosis? J Pediatr Neurosci 2020;15:128-31.
4. Ana SC, Tatiana VB, Vera CL, Saul Martins PM, Isabela PA. Moebius syndrome: A case with oral involvement. Cleft Palate Craniofac J 2008;64:371-2.
5. Abramson DL, Cohen MM Jr., Mulliken JB. Moebius syndrome: Classification and grading system. Plastic Reconstr Surg 1998;102:961-7.
6. Di Blasio A, Cassi D, Di Blasio C, Gandolfini M. Temporomandibular joint dysfunction in Moebius syndrome. Eur J Paediadr Dent 2013;14:295-8.
7. Towfighi J, Marks K, Palmer E, Vannucci R. Moebius syndrome. Neuropathologic observations. Acta Neuropathol 1979;48:11-7.
8. Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel-feel, and Mobius anomalies. Am J Med Genet 1986;23:903-18.
9. Nunes ML, Friendrich MA, Loch LF. Association of misoprostol, moebius syndrome and congenital central alveolar hypoventilation: Case report. Arq Neuropsiquiatr 1999;57:1-5.
10. Roca LT, Shylik AT, Jansen JG, Singh MK, Epstein JA, Altunoglu U, et al. De novo mutations in PLXND and REV3L cause Mobius syndrome. Nat Commun 2015;6:7199.
11. De Serpa Pinto MV, De Magalhaes MH, Nunes FD. Moebius syndrome with oral involvement. Int J Paediatr Dent 2002;12:446-9.
12. Pitner SE, Edwards JE, McCormick WF. Observations on the pathology of the Moebius syndrome. J Neurol Neurosurg Psychiatry 1965;28:362-74.
13. Srinivas MR, Vaishali DM, Vedaraju KS, Nagaraj BR. Mobius syndrome: MR findings. Indian J Radiol Imaging 2016;26:502-5.
14. John JS, Vanitha R. Case report-moebius syndrome with dandy-walker variant and agenesis of corpus callosum. J Pediatr Neurosci 2013;8:210-2.
15. Kulkarni A, Madhavi MR, Nagasudha M, Bhavi S. A rare case of Mobius sequence. Indian J Ophthalmol 2012;60:558-60.
16. Slee JJ, Smart RD, Viljoen DL. Deletion of chromosome 13 in Moebius syndrome. J Med Genet 1991;28:413-14.
17. Harbord MG, Finn JP, Hall-Craggs MA, Brett EM, Baraitser M. Moebius syndrome with unilateral cerebellar hypoplasia. J Med Genet 1989;26:579-82.
18. Gutman D, Sharon A, Laufe D. Moebius’ syndrome: Surgical management of a case. Br J Oral Surg 1973;11:20-4.
19. Gadoth N, Biedner B, Torok G. Mobius syndrome and Poland anomaly: Case report and review of the literature. J Pediatr Ophthalmostrab Strab 1979;16:374-6.
20. Kuhn MJ, Clark HB, Morales A, Shekar PC. Group III Mobius syndrome: CT and MRI findings. Am J Neuroradiol 1990;11:903-4.
21. Ha CY, Messiah ZS. Management of a patient with Mobius syndrome: A case report. Spec Care Dentist 2003;23:111-6.
22. Elsahy NI. Moebius syndrome associated with the mother taking misoprostol, moebius syndrome and congenital central alveolar hypoventilation: Case report. Arq Neuropsiquiatr 1999;57:1-5.
23. Budic I, Šurdilovic D, Slavkovic A, Marjanovic V, Simic MS. Moebius syndrome: Challenges of airway management. Acta Clin Croat 2016;55:94-7.
24. Krajcivir WJ, Azar I, Opperman S, Lear E. Anesthetic management of a patient with Möbius syndrome. Anesth Analg 1985;64:371-2.
25. Mussi MC, Moffa E, Castro T, Ortega AL, Freitas G, Braga M, et al. Salivary parameters and oral health in the Moebius syndrome. Special Care Dent Assoc Wiley Period 2016;36:265-70.
26. Terzis JK, Karypidis D. Neurotization DT. The effect on speech management of a case. Br J Oral Surg 1973;11:20-4.
27. Fernandes CR, Filho W A, Cezar LC, Gomes JM, da Cunha GK. Moebius syndrome: A rare entity or a missed diagnosis? J Pediatr 2013;102:961-7.

How to cite this article: Nagaraj T, Kongbraitapam S, Pai SA, Debnath P, Ramasamy P, Mumtaz S. Moebius syndrome: A review of literature. J Adv Clin Res Insights 2020;7(2):25-29.