Moebius Syndrome: A Rare Entity or a Missed Diagnosis?

Sreetama Chowdhury, Shatanik Sarkar, Debasuree Guha, Malay K. Dasgupta

Department of Paediatric Medicine, R. G. Kar Medical College and Hospital, 1Department of Paediatric Medicine, KPC Medical College & Hospital, Kolkata, West Bengal, India

INTRODUCTION

Moebius syndrome is an underreported and underdiagnosed neurological disorder, classically involving the sixth and the seventh cranial nerves. An International Group of Experts at the Moebius Syndrome Foundation in 2007 formulated a diagnostic criteria for diagnostic consistency, which include (1) Congenital facial diplegia or uniplegia, lower motor neuron type in nature, and (2) Paralysis of lateral movements of eyes and strabismus due to sixth cranial nerve palsy.[1] The dyad of congenital facial and abducens palsy was first described by Von Graefe in 1880 and Paul Julius Moebius in 1888, after whom the syndrome was eponymously named.[2] The syndrome may also include involvement of the other cranial nerves and various other congenital deformities and malformations. In spite of being a congenital disorder with all the features present since birth, diagnosis is often delayed, as suggested from the lower number of reports in the newborn period and infancy. In fact in India, less than five infant cases have been reported,[3-5] Our patient is probably the first infant case to be reported from eastern India.

CASE REPORT

A 1.5-month-old male infant, born out of a non-consanguineous marriage, presented to the outpatient department (OPD) of our hospital with poor weight gain and feeding problems. The child was admitted due to failure of postnatal weight gain (birth weight, 2010 g; admission weight, 1860 g). On detailed examination, there was obvious deviation of the angle of mouth to the right side, with the absence of nasolabial folds on the left side. Forehead folds were also notably absent on the left side during crying. There was associated deviation of the tongue toward the left side. Ocular findings included incomplete closure of the left eye and convergent squint [Figure 1]. No associated limb malformations or hypotonia were observed.

The child was born as a term, small for gestational age baby via normal vaginal delivery. Mother had a history of abortifacient usage in the first trimester of her pregnancy without any documentation. But, thorough history revealed usage of an oral drug for three consecutive days bought over the counter, likely to be a prostaglandin analog. Prenatal period was otherwise uneventful. No history of instrumental delivery or perinatal asphyxia was reported. Immediate postnatal period was also uneventful without any history of
convulsions, repeated vomiting, or persistent crying as stated by the mother.

As per the examination findings, which revealed multiple cranial nerve palsies (i.e., left facial nerve—LMN type, left hypoglossal nerve, and bilateral abducens nerve), magnetic resonance imaging (MRI) of brain was done. But, MRI was essentially normal, excluding the possibilities of any perinatal insult, space-occupying lesion, or structural anomaly. Nerve conduction velocity (NCV) test of facial nerves done at 6 months of age showed left-sided LMN type facial palsy, but it could not throw any light on the probable site of lesion [Figure 2]. In the absence of any detectable cause, diagnosis of Moebius syndrome was made.

Figure 1: Face of the baby showing (A) absence of nasolabial fold, forehead creases, and eye closure on left side, (B) deviation of tongue towards left, and (C) convergent squint

Figure 2: Nerve conduction velocity of facial nerve showing left-sided LMN type facial palsy
Feeding was established gradually with top feeding over and above breast feeding to ensure adequate weight gain. Mother was guided in attachment and feeding technique, keeping in mind the inherent problem of the child in effective sucking. Care of the left eye was provided in the form of artificial tear drops and patching the eyes during sleep for prevention of exposure keratitis. Multivitamins were supplemented, and the child was discharged after 1 week. Further follow-up in OPD showed good weight gain and subjective well-being of the child.

**DISCUSSION**

Moebius syndrome is an extremely rare congenital dysinnervation disorder characterized by bilateral or unilateral facial nerve weakness with bilateral abducens nerve palsy. It can be associated with other cranial nerve palsies such as trigeminal, oculomotor, auditory, spinal accessory, or hypoglossal; as well as multiple other defects such as malformed tongue, cleft palate, or micrognathia; skeletal malformations such as syndactyly or brachydactyly, scoliosis, arthrogryposis, absence of pectoralis muscles (Poland–Moebius syndrome), Kallmann syndrome, Pierre–Robin sequence, features of Carey–Fineman–Ziter syndrome; and skin manifestations such as café au lait spots and axillary webbing. There is diminished facial expression resulting in poor parental bonding. Autism spectrum disorders have widely been reported in the patients, amounting around 30%–40% according to a study by Ana et al.\[6\]

The etiology of this syndrome is a debatable issue with multiple postulated hypotheses. The suggested etiological factors include dysplastic or degenerative developmental disorders such as hypoxic–ischemic injuries, especially around 5–6 weeks of gestation, peripheral neuropathies, vasculopathies, gestational trauma, drug exposure, and a genetic component. In rare cases, alteration in the genes REV3L and PLXND1 has been implicated as causative of Moebius syndrome. The syndrome is also listed as Online Mendelian Inheritance in Man (OMIM) Number 15700, with a gene map locus of 13q12.2-q13.\[8\]

Exposure to infections, alcohol, cocaine, thalidomide, and misoprostol were also related to this syndrome. Of these, intake of misoprostol, frequently used for induction of abortion among pregnant mothers, has been widely reported in literature.\[9\] Misoprostol usage in the first 2 months of gestation may induce an ischemic event in the embryonic brain stem. There is a history suggesting intake of misoprostol by the mother in our case, though undocumented.

The incidence of Moebius syndrome is around 2–20 cases per million births.\[10\] There is no sex or ethnic predilection. A system of classification first reported by Towfighi et al.\[11\] based on the pathologic differences in the case reports has been postulated. It includes the following:

- **Group I:** Hypoplasia or atrophy of the cranial nerve nuclei
- **Group II:** Primary lesions in the peripheral cranial nerves
- **Group III:** Focal necrosis of the brain stem nuclei
- **Group IV:** Primary myopathy with no central nervous system (CNS) or cranial nerve lesions

Diagnosis of Moebius syndrome is mostly clinical, and no specific laboratory investigation is available for diagnosis. Computed tomography (CT) scan may show calcification at the site of ischemic necrosis in the brain stem, most commonly the dorsal pons. MRI may show brain stem hypoplasia or atrophy.\[12\] Role of NCV may be there to locate the site of lesion, but their usefulness is not yet well established. Routine stamping of all the facial palsies at birth as birth trauma should be avoided and thorough examination of all other cranial nerves may result in earlier diagnosis of this disorder. In our case, the persistence of the facial palsy beyond 6 weeks of life made it unlikely to be a traumatic facial paralysis due to birth injury. Hereditary-isolated facial palsy was also ruled out due to involvement of other cranial nerves.\[13\] Other differential diagnoses include hemifacial microsomia (Goldenhar syndrome), DiGeorge syndrome, and CHARGE syndrome, which were excluded due to the absence of associated features.

The management of Moebius syndrome requires a multidisciplinary approach. Infants require feeding assistance and thorough nutritional management to ensure adequate postnatal weight gain. Physical, speech, and occupational therapy helps in better motor control and betterment of speech and eating habits. Special attention must be provided to the eyes for the prevention of exposure keratitis. Strabismus and lagophthalmos are surgically correctable. A new surgical technique called “the smile operation” involves microvascular transfer of gracilis muscle to face and connects the nerves supplying the masseter. Other techniques include temporalis tendon transfer and bilateral selective neurolysis.

So, to conclude, early diagnosis of the cases by experienced clinicians and a supportive multidisciplinary approach can help children with Moebius syndrome lead a near-normal life.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Miller G. Neurological disorders. The mystery of the missing smile. Science 2007;316:826-7.
2. Pitner SE, Edwards JE, Mccormick WF. Observations on the pathology of the Moebius syndrome. J Neurol Neurosurg Psychiatry 1965;28:362-74.
3. Singh A, Sachan R, Rawat M. Moebius syndrome in an infant with fetal misoprostol and mifepristone exposure. Pediatr Oncall J 2016;13:44-5.
4. Taksande A. Möbius syndrome associated with acyanotic congenital heart disease in a neonate. J Mahatma Gandhi Inst Med Sci 2014;19:138-40.
5. Singh P, Gupta SB, Kumar R, Agarwal R, Singh DP, Verma D. Moebius syndrome: a case report. Int J Med Res Rev 2014;2:624-6.
6. Ana SC, Tatiana VB, Vera CLSR, Saul Martins PM, Isabela PA. Moebius syndrome: a case with oral involvement. Cleft Palate-Craniofacial J 2008;45:319-24.
7. Tomas-Roca L, Tsaiabi-Shytlik A, Jansen JG, Singh MK, Epstein JA, Altunoglu U, et al. De novo mutations in PLXND1 and REV3L cause Möbius syndrome. Nat Commun 2015;6:7199.
8. Moebius syndrome. Available from: https://www.omim.org/entry/157900. [Last accessed on 2019 Jan 17].
9. Pastuszak AL, Schüler L, Speck-Martins CE, Coelho KE, Cordello SM, Vargas F, et al. Use of misoprostol during pregnancy and Möbius’ syndrome in infants. N Engl J Med 1998;338:1881-5.
10. Serge O, Gaurav S, Sherri B. Mobius syndrome. Am J Neuroradiol 2005;26:430-2.
11. Towfighi J, Marks K, Palmer E, Vannucci R. Moebius syndrome: neuropathologic observations. Acta Neuropath 1979;48:11-7.
12. Volpe JJ, editor. Volpe’s neurology of the newborn. 6th ed. Amsterdam, The Netherlands: Elsevier; 2017. pp. 690-1.
13. Aslan N, Sivrice C, Ormeki AR. The differential diagnosis of a patient with unilateral congenital facial paralysis: 3q21 deletion. Acad J Pediatric Neonatol 2018;6:555743.