Moebius Syndrome as a Disorder of Neonatal Recurrent Aspiration

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Moebius syndrome (MBS) is a rare disease characterized by non-progressive congenital non-traumatic palsy of the facial and abducens cranial nerves and could be unilateral or bilateral.

A four-month-old boy with Moebius syndrome was transferred to the pediatric ICU with persistent respiratory acidosis and respiratory failure that required endotracheal intubation. Subsequently, he presented with aspiration pneumonia and sepsis, secondary to underlying central hypoventilation and aspiration. He is currently on long-term ventilation and aspiration prophylaxis.

This case reveals the association between Moebius syndrome and gastro-esophageal reflux disorder (GERD) with nocturnal central hypoventilation; it highlights the need for close monitoring and protection of the airways until the age of two years.

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Von Graefe and Möbius described the syndrome in the years 1880 and 1888, respectively[1]. The incidence ranges from 0.00002% to 0.002%[2]. Embryological development of the hindbrain (rhombencephalon) into the medulla, pons, and cerebellum is theorized to be anomalous in some cases of Moebius syndrome. Whereas in others, certain genes have been implicated. However, most cases are sporadic. Some authors prefer the term 'sequence' to the syndrome, as it defines a cascade of events secondary to an insult during embryogenesis[3,4]. These factors emphasize the variable clinical and genetic heterogeneity of this disorder.

The aim of this report is to present a case of Moebius syndrome associated with gastro-esophageal reflux disorder (GERD).

THE CASE

A four-month-old male who was born via spontaneous vaginal delivery at 37 weeks with a birth weight of 1.9 kg and an APGAR score of 7/8, no perinatal complications or NICU admissions. The baby presented with poor feeding, failure to thrive, and unilateral left-sided facial twitching. Family history did not include any congenital disorders or consanguinity. On inspection, the baby was febrile, irritable, and in respiratory distress. He was admitted with bronchiolitis and seizures for evaluation. Investigations revealed leukocytosis (22,000), lymphocytosis (54%), and elevated C-reactive protein (86). After admission, the child deteriorated clinically with evidence of persistently worsening respiratory acidosis, which eventually required endotracheal intubation. He remained intubated for 10 days; after which, he developed significant secondary supraglottic edema. It was apparent that the underlying cause was nocturnal central hypoventilation in combination with tracheal narrowing and GERD.

One month later, he presented with aspiration pneumonia, sepsis, poor feeding, and seizures. This was followed by a series of recurrent aspirations secondary to GERD and central hypoventilation. Subsequently, he was put on long-term tracheostomy. Moebius syndrome was suspected when the baby exhibited multiple cranial nerve palsies, craniofacial dysmorphisms, as well as orthopedic manifestations. The baby exhibited a squint, reduced visual acuity, and pallor of the discs (CN VI). The baby was unable to smile and had an expressionless face (CN VII). In addition, he failed the hearing test (CN VIII), and had an absent swallow and gag reflex with uncoordinated sucking (CN IX, X). Furthermore, he displayed orofacial deformities, including micrognathia, microstomia, and hypoplastic tongue (CN XII). The glabellar and corneal reflexes were positive. Musculoskeletal abnormalities comprised of bilateral congenital talipes equinovarus (CTEV) deformity and bilateral 'thumb-in-palm' deformity with the thumbs displaced proximally. MRI brain revealed evidence of diffuse corpus callosum hypoplasia, cavum septum pellucidum et vergae, and bilateral connatal cysts near the superolateral angles of the body and frontal horns of the lateral ventricles. Mega cisterna magna was found.

DISCUSSION

The etiology of Moebius syndrome remains controversial. The origin is a combination of epigenetic factors, environmental and genetic[1,3,5]. Moebius syndrome was traditionally thought of as a culmination of in utero events occurring in early gestation. The vascular hypothesis describes an insult of a vascular origin to the watershed zones of the lower brainstem[6,7]. This leads to cranial nerve nuclei hypoplasia and supranuclear pathway atresia, resulting in abnormal posturing of the fetus and pressure changes in the developing brain. Mobius syndrome is now considered a rhombencephalic disorder and a complex developmental disorder of the lower brainstem[6,8,9].

Three Moebius syndrome loci have been demarcated as MBS1-3. MBS1 at chromosome 13q12.2-q13; MBS2 called hereditary congenital facial paresis 1 (HCFP1) at 3q21-q22, and MBS3 (or HCFP2) at 10q21.3-q22.1. Patel et al associated de novo mutation of TUBB3 with corpus callosum agenesis, septum pellucidum absence, simplified gyral pattern, and miscellaneous brain malformations[1,10].

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Typical Moebius syndrome is classic cranial nerve VI/VII palsy, orofacial dysmorphisms, and chest/limb deformities. Differentiating typical and atypical presentations of Moebius is complicated by the wide array of possible clinical findings[1]. The lack of any investigative criteria or confirmatory genetic testing gives rise to diagnostic confusion; therefore, diagnosis is entirely clinical. In 2007, the Moebius Syndrome Foundation refined the diagnosis, labeling MBS as "congenital, uni- or bilateral, non-progressive facial weakness and limited abduction of the eye(s)" [11].

Disturbances in ocular motility, such as esotropia, exotropia, or gaze palsy can occur in Moebius syndrome[8]. Incomplete lid closure is a consequence of weakened eye closure (CN VII), relative to spared eye-opening (CN III), may lead to corneal ulceration as well as visual impairment[7,8]. Thoracic abnormalities, such as Poland anomaly, are commonly associated[8]. Additional cranial nerve abnormalities, such as CN VIII, IX, X, XI, and XII and the respective dermatomes and myotomes innervated maybe affected. The involvement of the cochlear CN VIII can result in linguistic delay[12]. Furthermore, oro dental problems may arise, such as cleft palate, mandibular hypoplasia, incompetent lip closure, and abnormal tongue movements[13]. Limb abnormalities such as clubfoot and digit deformities could be seen. Baraitser et al found significant developmental delay of 50%[14]. Epilepsy and autism spectrum disorders have also been linked[13,15]. There is no significant evidence that cognitive impairment is linked with Moebius syndrome[13].

Possible radiological findings in MBS include hypoplasia of pons and cerebellum and potential absence of the facial nerve[6]. Intra-axial brainstem calcifications could manifest later[16]. The MRI findings seen in our patient are considered atypical for Moebius syndrome[1]. The patient was too young to show any calcification or hypoplasia of the brain stem or cerebellum. Additionally, these findings suggest the involvement of TUBB3.

Feeding difficulty in Moebius syndrome is multifaceted. It is a combination of the difficulty of retaining food in the mouth, microstomia, hypoglossia that impedes food bolus manipulation, oromandibular hypoplasia, as well as pharyngeal plexus dysfunction secondary to lower cranial nerve palsies (CN IX, X, X)[8]. GERD secondary to impaired lower esophageal sphincter tone and inability to swallow or cough out oral secretions lead to aspiration and long-term airway dysfunction[15,17-19]. These phenomena are thought to be secondary to the congenital hypoplasia or necrosis of the respiratory centers leading to abnormal central respiratory drive and alveolar hypoventilation[15,20].

Short-term management primarily involves managing the underlying causes namely GERD and nocturnal central hypoventilation. The aim should be to minimize aspiration secondary to the palatopharyngeal dysfunction in our patient. Anti-reflux formula and agents such as glycopyrronium are recommended to help reduce oral and pharyngeal sections. Moreover, chest physiotherapy and caffeine citrate are useful to minimize apnea and improve respiratory function. It is essential to promote and monitor the growth using high caloric formula. Continuous seizure prophylaxis and tracheostomy placement, in this case, are needed to stabilize the patient before he could maintain ventilation independently.

Long-term management and a multidisciplinary approach by pediatricians, radiologists, neurologists, ophthalmologists, orthopedic surgeons, dental and plastic surgeons, genetic counselors, speech and physical therapists are of paramount importance. This must include gaze correction, smile and strabismus surgery, and ptosis repair, if present. In addition, physical therapy can improve facial muscle function via possible haphazard innervation of the facial muscles by other cranial nerves[6,21]. Much like other myopathic disorders, we risk rhabdomyolysis, malignant hyperthermia, and hyperkalemia with agents such as succinylcholine[15]. Additionally, Krajcirik et al warn against the use of anesthetic agents and neuromuscular blocking agents (NMBAs) as they may exacerbate respiratory insufficiency, especially if hypotonia is involved[15]. Hence, short-acting anesthetic drugs are recommended[22].

CONCLUSION

The lack of standardized minimal diagnostic criteria obscures clinical diagnosis.
A multidisciplinary clinical approach is advised regarding both the diagnosis and management of Moebius syndrome.

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