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MOEBIUS SYNDROME

Ophthalmology

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KEYWORDS

INTRODUCTION

Moebius syndrome is a disease that is characterized by congenital unilateral or bilateral non-progressive palsy of facial and abducens nerves i.e cranial nerves VI and VII. It leads to unilateral or bilateral weakness of the face along with limited abduction of the eyes. Facial weakness generally includes the inability to smile, chew or close the mouth, drooling and difficulty sucking. Palsies of other cranial nerves can also lead to moebius syndrome such as CN XII, X, IX, III, VIII, V, IV and XI.

In 1880, first case of this rare disease was described a merger of congenital 6th and 7th nerve palsy by A. Von Graefe. After eight years in 1888, The honor of naming it as "Moebius syndrome" was provided to a German neurologist Paul Julius Moebius because of his contributions via reports on the clinical features of ophthalmoplegia associated with this disease. (1)

Epidemiology And Etiology

The assessment of Moebius syndrome is quite difficult because of the uncertainties in the expertise and diagnostic methodologies or criterias. But since the establishment of Moebius Syndrome Foundation at Bethesda convention in 2007 the average age of diagnosis has been drastically reduced from 3.4 years to 2.2 years of age. The prevalence rate of Moebius syndrome is estimated to be 1/250,000. Most of the cases are sporadic, but 2% of all reported cases represent a familial background which leads to a controversial debate on whether this disease has a genetic Etiology or not. Even though the causes and pathogenesis are unknown right now, some authors and researchers have concluded that genetically determined vascular rhombencephalic developmental disturbances, acquired ischemic events after 5th week of gestation and fetal toxic exposure are some of the risk factors of this disease. (2,3)

The most widely accepted hypothesis regarding the etiology of Moebius syndrome is hypoxic ischemic insult to the developing Brain Stem especially after 5 weeks of gestation or intrauterine development. According to the distribution of Basilar artery (i.e. branch of vertebral artery), the most susceptible area for this ischemic insult is the dorsomedial area of the brain stem. This ischemic insult, specifically to the subclavian region during the 6th week of intra-uterine life results in abnormal development of the brain stem. The causes for this disruption can be either fetal or maternal. The fetal causes include thrombus formation, embolism, intrauterine trauma or hemorrhage or infections while the maternal causes include hyperthermia, use of certain drugs like misoprostol, thalidomide, ergotamine, benzodiazepines or cocaine and alcohol abuse.

But this hypothesis does not explain the defects found in the facial and abducens nerves because these areas do not have subclavian arteries as their blood supply. (4)

Genetic Etiology of Moebius Syndrome is another hypothesis that is also widely accepted. At 3q21-q22 and 10q, two genetic loci have been located in association to Moebius syndrome. It is mentioned in the Online Mendelian Inheritance in Man (OMIM) number %157900, with a gene map locus of 13q12.2-q13. A "%" preceding the entry number denotes that the entry refers to a confirmed Mendelian phenotype or its locus for which the responsible molecular relevance is not known. (5)

Clinical Features

The most common presentations in Moebius Syndrome include the irregularities and deformities due to facial (CN VII) and abducens nerves (CN VI). Usual incomplete bilateral involvement of CN VII leads to disturbed facial sensations, speech, ability to feed and expressions. Several orofacial deformities have also been noted in some cases which include cleft lip and palate, underdeveloped maxilla, micrognathia, mirco/aglossia, hypertelorism and certain dental problems.

Involvement of CN VI leads to ocular manifestations like lateral gaze palsies, ptosis, strabismus, ophthalmoplegia and these conditions further lead to exposure keratopathy.

The involvement of cranial nerves further aggravate the situation of the patient to the point where there are functional problems in breathing and swallowing. There is delayed onset of lacrimation along with crocodile tear phenomenon, epiphora and dry eyes. Refractive errors are also common in patients of Moebius syndrome with the most common one being compound hyperopic astigmatism.

On analyzing the data of several studies it was concluded that ocular manifestations can be categorised into 3 groups or patterns:

1. **Pattern A:** Complete defect in both abduction and adduction ocular movements accompanied with orthotropia in the primary position.
2. **Pattern B:** A large-angle esotropia, crossed fixation and a comparatively decreased abnormality in convergence and adduction.
3. **Pattern C:** A large-scale exotropia in the primary position with torticollis, vertical ocular misalignment and absence of convergence.

Apart from ocular and facial symptoms, Moebius Syndrome also presents with musculoskeletal manifestations which include Clubfoot, syndrome/ brachy/ ectrodactyly, kyphosis, scoliosis, rib defects etc.. These musculoskeletal manifestations are only seen in sporadic forms and are rather absent in the familial cases of this disease.

Table no.1: The System Devised by Abramson et al. to Classify the Extent of MBS Marked by Morphological Deformities. (1)

	0	1	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

Diagnosis

As there is no specific criteria for diagnosing this disease, it is often misdiagnosd for some other similar syndrome. Genetic testing is available but with a drawback of being highly expensive and not easily accessible.

A Minimum Diagnostic Criteria for Moebius Syndrome was determined in 2007 which includes :

1. A non-progressive lower motor neuron type, unilateral or bilateral, symmetrical or asymmetrical congenital facial palsy.
2. Symmetrical or asymmetrical, unilateral or bilateral abducens (CN VI) nerves palsy.

It is necessary for both of these criteria to be met for a case to be diagnosed as Moebius Syndrome case.

Radiological findings can also help in diagnosis of this disease, especially CT brain, because it shows the calcification in the ischemic necrotic area on the dorsal aspect of pons where the region of abducens nerve is located.

Similarly, MRI brain of these patients also reveal the calcification along with cerebellar hypoplasia and atrophy of the brain stem that further confirms the absence of facial colliculus.

Moebius Syndrome is a diagnosis based on exclusion priciple which means after excluding similar syndromes the diagnosis of this disease is concluded. It is also important for clinicians and physicians to understand the patient's condition, as they have a blank expressionless face and fixed gaze, they are wrongly diagnosed as patients of mental disorders.(3)

Treatment

As there is no specific treatment for this congenital condition, only rehabilitation is the way by which modern medicine can help the patients of Moebius Syndrome. The recommended therapies include early initiation of speech along with physical rehab that can help to improve the speech, language swallowing and motor coordination skills. Surgical interventions can be used to improve the lifestyle of patients who also suffer from associated orofacial and limb deformities.

Early ophthalmological assessment can help rectify and assess the need for surgeries for the correction of strabismus and thus further help to reduce the progression of ocular manifestations into exposure keratopathy.

By following one's personal need and functional assessment, the rehabilitative approaches should be personalized to each patient. The physical and psychological deficits can be managed by using a multidisciplinary approach with a pre-established standard set of guidelines.

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