CASE REPORT

Möbius sequence with prenatal exposure to misoprostol

ABSTRACT

Objective
To present 3 cases of Möbius sequence exposed in utero to misoprostol and discuss their clinical presentations, etiopathogenesis, and management.

Methods
Medical records of 3 patients with Möbius sequence and prenatal exposure to misoprostol were reviewed. Clinical findings were compared with those reported in the literature.

Results
Lack of facial-muscle movement, lagophthalmos with secondary exposure keratitis, decreased ability to crease forehead, and shallow nasolabial fold imply facial-nerve dysfunction. Small- and large-angle esotropia and apparent orthotropia with abduction limitation showed varying degrees of abducens nerve involvement. Two patients had early prenatal exposure to misoprostol during the first 3 months of gestation.

Conclusion
A history of misoprostol exposure should be routinely elicited from parents of children with Möbius sequence. Associated deficiencies in Möbius sequence and its variants require a multidisciplinary approach.

Keywords: Cranial-nerve-VI and -VII palsy, Möbius sequence, Möbius syndrome, Misoprostol, Abortion
WITH steadily increasing rates of unwanted pregnancies, many unprepared mothers attempt abortion. Misoprostol (Cytotec), a prostaglandin analog used to treat gastric ulcers, is commonly exploited for its abortifacient properties. Recent studies have described Möbius sequence, a congenital nonprogressive sixth- and seventh-cranial-nerve palsy, among infants exposed in utero to the drug during unsuccessful abortion.1-3

CASE REPORTS
In this study, we present 3 such cases of Möbius sequence following prenatal exposure to misoprostol.

Case 1
A two-year-old girl was referred to the ophthalmology department of the University of the Philippines–Philippine General Hospital (UP-PGH) for evaluation for Möbius sequence. She was born full term to a 20-year-old primigravid. She was small for gestational age, weighing 2,050 grams. Apgar score was 9. At 1 month age of gestation (AOG), the mother attempted abortion with misoprostol 200 mg/tab, taking 1 tablet orally and inserting 1 tablet intravaginally. At birth, inversion of both feet, small head circumference, and mild dilatation of lateral ventricles with absent corpus callosum on cranial computed tomography were noted. Developmental milestones were markedly delayed. Intermittent esotropia (ET) was observed at 1 month of age.

On ophthalmologic examination, dazzle testing for both eyes was unreliable due to weak and inconsistent lid closure to bright halogen light. There was central steady fixation on vertical gaze with slight left-eye preference. Horizontal gaze could not be assessed. Full cycloplegic refraction (FCR) with atropine was +1.00 diopter sphere for both eyes. Epicanthal folds and lagophthalmos were observed. The patient had 10- to 15-degree ET by Krimsky with slight left-eye preference (Figure 1A). Minimal eye movement on up- and downgaze was noted (Figure 1B). This was confirmed by the presence of doll’s eye reflex for vertical gaze which was not apparent on lateral gaze. On biomicroscopy, there was punctate dye uptake in the central inferior 1/3 of the cornea. The rest of the eye examination was unremarkable.

Patient was started on eye lubricants 2 times/day. The preferred eye was patched. After evaluation by the other subspecialty clinics, follow-up was advised.

Case 2
The patient was an eight-year-old boy whose mother allegedly attempted abortion with intake of misoprostol at 5 months AOG. There is a 55 PD ET by Krimsky testing (A), and limited abduction on duction and version in both eyes (B).

Case 3
An 18-month-old boy whose mother attempted abortion with intake of 2 tablets of misoprostol for 3 consecutive days. He is orthotropic on primary gaze with no lateral eye movements in both eyes (A), and has talipes equinovarus of the right lower extremity (B).
autism and global developmental delay. At 5 months of age, there was alternating intermittent ET, which became permanent at around 5 years of age. Systemic evaluation showed multiple congenital anomalies (esotropia, micrognathia, epicanthal fold, microcephaly, undescended testes).

On initial ophthalmologic consultation, visual acuity (by LEA chart) was at least 20/80 in each eye. Full cycloplegic refraction was +1.00 diopter sphere in the right eye and −1.00 diopter sphere in the left. He had prominent epicanthal folds. No lagophthalmos was observed. There was alternating esotropia, with 55 prism diopter by Krimsky testing (Figure 2) and left-eye preference. Limited abduction was observed in both eyes onduction and version. Anterior-segment and fundus examinations were normal. Shallow nasolabial folds were present with limited ability to raise the forehead.

A medial rectus recession in both eyes was recommended. Patching of the left eye 4 hours a day was advised. Remeasurement of the deviation prior to the contemplated muscle surgery was also recommended.

Case 3
The patient was an 18-month-old boy referred for visual prognostication. The patient was born full term via spontaneous vaginal delivery to a 35-year-old G4P3 (3-0-0-3) mother who took 2 tablets of misoprostol (200 mg/tab) orally per day for 3 consecutive days 1 month into the pregnancy. Minimal vaginal bleeding was noted but pregnancy continued and progressed to term. At birth, right club foot was observed (Figure 3B). Consultation at UP-PGH showed talipes equinovarus, shallow left nasolabial fold, left-lid lag, mask-like facies, and limited extraocular movements. Möbius sequence was considered. He was referred to pediatrics, orthopedics, neurology, ENT, and ophthalmology for further evaluation. He underwent serial casting and percutaneous tenotomy of the right foot at 3 months of age.

On ocular examination, dazzle reflex could not be clearly elicited. There appeared to be good central fixation in both eyes. Horizontal eye movements could not be assessed due to lack of lateral gaze. Although the patient seemed to have right-eye preference, this was not consistent and reliable. Red-orange reflex was symmetrical on Bruckner’s test with a short acting cycloplegic refraction of −2.50 diopter sph −1.00 diopter cyl x 180 and −2.50 sph. The eyes were orthotropic on primary gaze. There was mild limitation on abduction with a 10 prism diopter esotropia by Krimsky and exotropia on downgaze. Anterior- and posterior-segment examinations were unremarkable. No surgical intervention was considered. Spectacle correction and monitoring for amblyopia were recommended.

Patient also had recurrent bouts of pneumonia and died of respiratory failure at age 2 years and 2 months.

**DISCUSSION**

In the clinical setting, the constellation of findings of large-angle esotropia with various gaze palsies, associated with mask-like facies, incomplete eyelid closure, prominent upper lip, inability to close the mouth, drooling, poor suck, and speech

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¹Central, steady, maintained
²Brainstem-auditory-evoked response
impairment raises a high index of suspicion for Möbius sequence, a disorder primarily involving the facial and abducens motor nerves.

Ocular conditions that may present with large-angle esotropia with limited lateral rectus function include congenital sixth-cranial-nerve palsy, congenital infantile esotropia, and Duane syndrome. These conditions, however, do not have signs and symptoms characteristic of facial-nerve involvement as seen in Möbius sequence.

Möbius sequence is a rare disorder, occurring in 1 of every 50,000 live births with no sex predilection. Von Graefe initially described a patient with congenital facial diplegia in 1880 but Paul Julius Möbius, a German neurologist, reviewed more cases and reported an association with congenital, nonprogressive bilateral facial and abducens nerve palsy along with other systemic abnormalities. Several diagnostic criteria since then have been proposed. The latest was by Verzijl who suggested facial palsy with impairment of ocular abduction as the primary criterion for Möbius syndrome. The distribution of the facial-nerve dysfunction with more severe involvement of the upper facial muscles and a relative sparing of the lower facial muscles, plus the inability to abduct the eye beyond the midline (usually bilateral and complete), are highly characteristic of the syndrome. Features commonly associated with Möbius syndrome, but are not essential for diagnosis, are listed in Table 2. Frequently mentioned in the literature was Möbius-Poland syndrome or Hanhart syndrome, which is descriptive of patients with dysfunction of cranial nerves VI and VII associated with extensive limb anomalies (in contrast to Möbius syndrome which consists primarily of cranial-nerve deficits). The third patient showed traits of this syndrome variant, being diagnosed with talipes equinovarus at birth and subse-
quent undergoing corrective orthopedic surgery.

Involvement of the other cranial nerves led to significant speech and feeding problems. Bulbar weakness, especially cranial nerves IX and X, may cause dysphagia. The hypoglossal nerve was the third most commonly affected, often leading to tongue atrophy with inability to protrude the tongue beyond the lips.

Associated neuropsychiatric disorders included autism and mental retardation, seen in 24.7 to 28.5% and 10 to 75% of patients, respectively.

Ocular features associated with Möbius sequence have been studied extensively (Table 3), with few cases involved in most series (Table 4).

Common ocular findings included esotropia and abduction limitation, characteristics essential to the inclusion criteria in most studies. These were usually observed within the first 6 months of life, and in approximately 50% of cases, abducens-nerve palsy was the only ocular palsy. A face turn was sometimes present on primary gaze and attempted lateral gaze. Large-angle esotropias have been reported, some measuring up to 100 prism diopters. Vertical and convergence ability were usually intact. When the third or fourth cranial nerves were involved, incomplete or complete ophthalmoplegia was sometimes present. Exotropia and orthotropia have been seen in a minority of patients. In this study, 2 patients had esotropia while the other was orthotropic on primary gaze. All presented with abduction limitation; 1 patient also had adduction limitation and the third had exotropia on downgaze only.

Seventh-cranial-nerve palsy usually causes facial weakness. This may manifest soon after birth as difficulty in sucking, drooling, and incomplete closure of the eyelids during sleep. Sometimes, facial paralysis may not be noticed until a few weeks or months later when the infant’s inability to smile or lack of facial movement with crying arouses the parents’ concern. Inability to close the mouth with prominence of the upper lip, lack of tissue sagging and wrinkling cause the distinctive “mask-like” facies. Verzijl and colleagues observed that 62% of patients had incomplete unilateral facial-nerve palsy, primarily affecting the upper face with relative sparing of the lower cranial-nerve muscles. In contrast, Santiago and Uy reported that all their patients had bilateral complete facial diplegia. Associated lagophthalmos, postulated to be from aberrant innervation of the orbicularis oculi muscle in 68 to 71.4% of patients, have been observed in 2 studies. Although exposure keratitis was commonly seen with lagophthalmos, this was not reported in any of the 4 case series probably due to bilateral Bell’s phenomenon. Epicantus was also a common finding. Various refractive errors were present and in the Cronemberger study, there was a positive correlation between reduced visual acuity and mental retardation. In this study, only 1 patient presented with complete facial diplegia and lagophthalmos. Two of the 3 patients had epicantus. Cycloplegic refraction was acceptable for age.

A history of prenatal misoprostol exposure in Möbius sequence has been reported in 18.8% of patients. Other studies reported various adverse antenatal events. In this series, all 3 patients had prenatal exposure to misoprostol. Since June 2005, 14 cases of Möbius syndrome have been seen at the UP-PGH pediatric ophthalmology clinic, 5 (35.7%) of whom had a history of prenatal exposure to the drug.

The etiopathogenesis of Möbius sequence is still unclear. Studies have proposed genetic and ischemic causes, teratogens being implicated in both. The term Möbius syndrome has been replaced with Möbius “sequence” to represent a pattern of multiple anomalies derived from a single structural defect or mechanical factor, usually due to multiple etiologies. This is in contrast to “syndrome,” which implies a single cause.

Genetic research has localized point mutations for Möbius sequence which affect cranial-nerve-nuclei development and axonal transport. Verzijl proposed lowerbrainstem maldevelopment to explain facial and abducens-nerve palsy, as well as motor-function deficits seen in many patients with Möbius sequence confirmed by imaging and EMG studies. The ischemic theory supposes an ischemic event in the lower brainstem causing disruption of its blood supply during the early embryonic period. Studies have implied in utero exposure to various teratogens, including misoprostol, in Möbius sequence presumably caused by constriction of uterine vessels.

Misoprostol is a prostaglandin E1 agonist used in the prevention and treatment of gastric NSAID-induced ulcers. Its uterotonic and cervical ripening actions make it an important drug in obstetrics for medical abortion and induction of labor. But this is also why it is exploited and misused for pretermination of unwanted pregnancies.

Congenital anomalies, including Möbius sequence, associated with misoprostol use in failed abortion attempts have been documented. Case series by Gonzales reported Möbius sequence in 4 of 7 (53.1%) and 17 of 47 (36.7%) of newborns exposed to misoprostol around 2 months AOG. A cohort study done by Pastuszak showed that attempted abortion with misoprostol was associated with a significantly increased risk for Möbius sequence. Among the mothers of patients with Möbius sequence, 47 (49%) had used misoprostol compared with 3 (3%) mothers from the other study group.

Studies have hypothesized that misoprostol’s uterotonic effects cause constriction of the uterine vessels, interrupting blood supply to the primitive subclavian artery.
with ischemic damage to the prenatal brainstem and other involved embryonic end organs.\textsuperscript{10} The sixth and seventh cranial nerves are commonly affected possibly due to their rhombencephalic position, a flexure point of the embryo when misoprostol affects a uterine contraction.\textsuperscript{10} Neuropathological studies support this theory, where ischemic-anoxic foci of gliosis, necrosis, and calcification were noted from the dorsal pons to the medulla, involving some cranial-nerve nuclei.\textsuperscript{5}

A study by Stromland and colleagues\textsuperscript{2} of 25 patients with Möbius sequence noted abnormal patterns of tearing; 6 patients, also diagnosed with autism, did not exhibit emotional tearing. This was a similar finding in a study on thalidomide embryopathy, where subjects who had sixth- and seventh-cranial-nerve palsy also had a high frequency of aberrant tearing. Abnormal lacrimation is an unusual finding but may exist more frequently than previously reported, as there is often no specific inquiry made regarding lacrimation. It is postulated to result from aberrant innervation of the lacrimal gland. The nucleus for lacrimation is situated in the brainstem close to the nuclei for cranial nerves VI and VII, a location that could possibly explain its association with palsy of the sixth and seventh cranial nerves.

There is no difference in the ophthalmologic management of patients with Möbius sequence with known \textit{in utero} exposure to misoprostol versus those with or without other known prenatal risk factors.

Nonsurgical ophthalmologic management includes detection and treatment of amblyopia, giving best correction, and prevention and treatment of primary and secondary dry-eye conditions. Full cyclopegic refraction and patching are usually initially employed to correct errors of refraction and deviation. Eye lubricants are given to prevent corneal decompensation.\textsuperscript{5}

There is no single surgical approach to correct strabismus of patients with Möbius sequence. The most important factor in surgical planning is the degree of residual abducting power present. These patients often have severely impaired or lack any abduction ability with secondary medial rectus muscle contracture. Surgical options include LR recessions/augmentations, transpositions, and MR injection of Botulinum toxin.

In summary, attempted abortion with misoprostol is associated with an increased risk of Möbius sequence in infants. It is not uncommon that such patients are initially brought in for consultation for their ophthalmologic condition. A history of misoprostol use for failed abortion should be routinely elicited. Aside from strabismus evaluation, work-up should include testing for primary tear dysfunction (from aberrant cranial-nerve-V innervation) as well as secondary causes of dry eye and associated complications.

Besides treating specific eye problems, recognizing key signs and symptoms and associated risk factors is important in identifying patients suspected to have Möbius sequence. Associated deficiencies in Möbius sequence and its variants require a multidisciplinary approach from different subspecialties. Parent counseling and education are invaluable. The public should be educated on the potential teratogenic effects of misoprostol in order to reduce its use as an abortifacient.

\textbf{References}


