MOEBIUS SYNDROME IN AN INFANT WITH FETAL MISOPROSTOL AND MIFEPRISTONE EXPOSURE

Abstract
Moebius syndrome is a rare entity characterized by unilateral/bilateral cranial nerve palsies and limb malformations. Etiology is largely unknown. We describe a case of Moebius syndrome who had bilateral cranial and abducens nerve palsies and bilateral congenital talipes equino varus with possible cause being fetal misoprostol and mifepristone exposure.

Introduction
Moebius syndrome is a rare entity, characterized by congenital non-progressive complete/partial, unilateral/bilateral cranial nerve palsy with or without other cranial nerve palsies and limb malformations (syndactyly, brachydactyly, absent digits or talipes), cleft palate, micrognathia, microtia, scoliosis, pectoralis hypoplasia or other chest wall deformities. (1) Etiology is unknown, probably involving transient ischemia, infections, genetic etiologies and abortifacient (prostaglandin E1). (4) We present a case of Moebius syndrome due to failed abortion at 6 weeks of gestation due to use of misoprostol and mifepristone.

Case Report
A 1 year old female child presented with acute gastroenteritis. On examination, she was noticed to have failure to thrive (weight 3.8kg, length 60 cms and head circumference 48cms) with global developmental delay. She had bilateral facial palsy, left corneal opacity, bilateral convergent squint suggestive of bilateral sixth cranial nerve palsy, left eye microphthalmia and microcornea, and bilateral club-feet. On inquiry, it was found that mother had taken oral mifepristone 600 µg at 6-week gestation for elective abortion and 2 days later had taken misoprostol 400 µg. One month later, despite significant metrorrhagia, an ultrasound examination showed ongoing pregnancy, with no anomalies observed in the fetus. So, pregnancy was continued. Antenatal ultrasound (USG) at 37 weeks gestation showed oligohydramnios with hydrocephalus. The child was born at term, and had a birth weight of 3.2kg. Parents had noticed bilateral congenital talipes equino varus (CTEV) at birth for which an orthopedic surgeon applied a cast. Parents also noticed that baby had feeding difficulty, poor development and facial dysmorphism but they did not seek medical attention for these. On presentation to us, we did MRI brain that showed communicating hydrocephalus. USG abdomen was normal. Chromosomal analysis could not be done because of financial concerns. Diarrhea subsided on oral rehydration therapy and patient was discharged and advised regular follow up.

Discussion
Moebius syndrome is a rare disorder first described by Von Graefe in 1880 and identified and defined in 1888 by Paul Julius Moebius. It consists of congenital unilateral or bilateral palsy of the abducens (VI) and facial (VII) cranial nerves. (1) It also involves abnormalities of the limbs, chest wall, spine, and soft tissues. Abramson et al actually classified and graded the syndrome on the basis of the clinical findings of cranial nerve palsies and musculoskeletal anomalies by using the acronym CLUFT (cranial nerve, lower limb, upper limb, face, and thorax). (3) This grading system included cranial nerve features of either partial or complete 6th or 7th nerve palsies or both; lower extremity findings of talipes equino varus, ankylosis, longitudinal, or transverse deficits; upper extremity involvement with digital hypoplasia or failure of formation; structural facial findings of cleft palate, micrognathia, or microtia; and thoracic findings of scoliosis, pectoral hypoplasia, or other chest wall deformity. Mental retardation and autism were also observed by some authors in one-third of a population of 25 patients with Moebius syndrome. (4) Our patient had bilateral VI and VII nerve palsies with congenital talipes equino varus. Hydrocephalus and microphthalmia was also seen in our patient. Intense vasoconstriction and uterine contraction caused by misoprostol resulting in hypoxia may explain this finding. (5,6) The etiology of Moebius syndrome is multifactorial, and several theories have been proposed, with the most supported theory being that of transient ischemic or hypoxic insult to the fetus. (3) Other infectious and genetic etiologies have also been proposed. In addition, the use of misoprostol, a prostaglandin-E1 analogue and abortifacient during pregnancy has also been implicated. (2) Use of oral or vaginal misoprostol during the first trimester of pregnancy significantly reduces uterine arterial blood flow. Doppler resistance indices are significantly increased 60–90 minutes after misoprostol administration (200 µg orally, or 200 µg intra-vaginally plus 200 µg orally) to pregnant women. (7) There are few case reports of Moebius syndrome secondary to the administration of misoprostol. (2,8–12). In several case reports, pregnancies not successfully aborted with mifepristone continued to full term with no adverse effects on the newborn. (13,14) Bernard et al (2013) conducted the first prospective study which found that the rate of major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2–3% rate in the general population. (15)

Thus we conclude that extreme care should be given to pregnancies that continue despite misoprostol administration, especially when exposure occurs between 5 and 8 weeks of gestation. Precise ultrasonography should be performed to detect any malformations possibly related to misoprostol exposure (e.g. limb defects), although it is almost impossible to detect cranial nerve palsies of Moebius syndrome before birth. Women considering medical abortion with the combination of mifepristone and misoprostol should be precisely counseled on the risks to their fetus if abortion failure occurs and surgical abortion is not desirable.
Authors Contribution
AS and MR conceived and drafted the study. AS will act as guarantor of the study. RS also designed the case report and revised the manuscript for important intellectual content. Final manuscript was approved by all the authors.

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