A woman presented at 33 weeks gestation with reduced fetal movements and a nonreactive nonstress test. Fetal ultrasound examination revealed a peculiar unilateral arm tremor. At emergency cesarean section, performed for fetal indications, a 1,672-gm male infant was delivered requiring intubation for feeble respiratory effort. After delivery the neonate was transiently hypertonic and later hypotonic. Continuing ventilatory support at minimal settings was necessary. The work-up for aneuploidy, metabolic disorders, and infection was negative. The infant died after being removed from ventilatory support on day 22. Postmortem examination revealed extensive bilateral brain gliosis and mineralization without evidence of inflammation, partial absence of cranial nerve nuclei III-XI, and a total absence of cranial nerve roots VI-XI. Together these findings are compatible with a diagnosis of expanded Möbius syndrome. © 2001 by Elsevier Science Inc. All rights reserved.


Introduction

Bilateral paralysis of cranial nerves VI and VII resulting in facial diplegia and restricted horizontal eye movement [1] commonly typify Möbius syndrome. Histopathology reveals diminution of cranial nerve nuclei with concurrent gliosis and mineralization. Other cranial nerves may be involved [1]. There may be associated craniofacial, skeletal, and other anomalies [1]. A case report of expanded Möbius syndrome involving cranial nerves III-XI, the brainstem, and portions of the spinal cord is presented.

Case Report

The mother of the patient, a 34-year-old gravida I Japanese woman, presented at 23 weeks gestation after having received her previous prenatal care in Japan. The pregnancy was uncomplicated until 33 weeks, when the mother noted decreased fetal movement. A nonstress test was nonreactive with a baseline fetal heart rate of 165 beats per minute and decreased beat-to-beat heart rate variability. The biophysical profile performed immediately thereafter was markedly abnormal, demonstrating no fetal movement, tone, or respiratory effort. The mother’s score was two (of eight) points for adequate amniotic fluid, Abnormal posturing of the left arm and hand was noted, with the arm flexed at the elbow and the hand fistled. Intermittent high-frequency tremors (about four per second) of the arm were noted, each lasting approximately 10 seconds. Amniocentesis was performed for evidence of bacterial or viral infection and fetal karyotype. All studies returned normal. Continuous fetal heart rate monitoring remained nonreactive in association with baseline tachycardia and poor beat-to-beat variability. An oxytocin challenge test was performed, which was negative. After a repeat biophysical score performed 2 hours later revealed no improvement, it was decided to proceed with primary cesarean section.

A 1,672-gm male infant was born with Apgar scores of one and six at 1 and 5 minutes, respectively. Umbilical arterial blood pH was 7.35. Poor respiratory effort of the infant was noted at birth and required intubation. Except for the neurologic findings, the infant’s initial vital signs and physical examination were normal. Neurologic examination revealed a hypertonic infant with little spontaneous movement. There was minimal withdrawal of the extremities to painful stimuli, and the Moro reflex was poor. Pupils were fixed and dilated, and there was no blink reflex to light. Suck and gag reflexes were absent. There were no facial or tongue movements. Extremities manifested hypertonicity and spontaneous clenches after painful stimulation, which was more marked in the lower extremities. The upper extremities were held internally rotated with flexion of the wrists. Seizure activity was not observed. Placental histology was normal.

Within hours of birth the infant was weaned to minimal ventilator settings and maintained in room air. There was mild metabolic acidosis, with blood lactate levels reaching 4.3 mEq/L, which was treated with bicarbonate infusion. Liver function tests were slightly elevated (aspartate transaminase = 192 U/L, low-density lipoprotein = 1,121 U/L, and γ-glutamyltransferase = 269 U/L) but these normalized, as did the metabolic acidosis, by day 12 of age. Peak bilirubin was 14.4 mg/dL. Urine amino acids, plasma long-chain fatty acids, uric acid, pyruvate, amino acids, carbohydrate deficiency glycoprotein assay, and plasma ammonia were normal. Blood and urine Cytomegalovirus cultures and serum toxoplasmosis titers were negative.

The infant’s neurologic status remained unchanged throughout his hospital course. Head ultrasound was normal. Cranial computed tomography (CT) scan revealed widened ventricles, widened sulci, and an increase in subarachnoid space, suggesting diffuse cerebral atrophy. Magnetic resonance imaging (MRI) studies were similar to the CT findings and revealed no additional pathologic findings. Electroencepha-
lography was normal. It was the impression of the pediatric neurologist consultant that the infant’s condition was most consistent with an expanded Möbius syndrome, with diffuse cranial nerve and brainstem involvement. The infant remained intubated and on the ventilator without improvement for 21 days. After extensive discussion with the parents, on day 21 he was extubated and died the next day.

Postmortem examination revealed that the infant died from acute bilateral bronchopneumonia, secondary to aspiration. The remainder of the examination was unremarkable except for the central nervous system. The brain weighed 283 gm (normal weight $= 278 \pm 96$ gm; mean $\pm$ S.D.) with a normal external appearance (even with the suggestions of atrophy on CT). Cranial nerve rootlets VI-XII were not present. The spinal cord appeared grossly normal. Microscopic sections of the diencephalon, midbrain, pons, medulla, and some areas of the spinal cord revealed diffuse gliosis with loss of neurons (Fig 1). In some areas, there are only residual, mineralized neurons remaining, as observed in the thalamic nuclei in Fig 2. The neurons in the nuclei of cranial nerves III-XI were almost entirely absent. The nucleus of cranial nerve XII was identifiable but scantily populated. The medial inferior olive and dentate nucleus was markedly gliotic with residual, mineralized neurons. In the pons and midbrain the tegmental areas were again markedly gliotic with mineralized neurons, but the pontine nuclei and substantia nigra were spared. The thalamic nuclei and basal ganglia were involved most severely, with near-total obliteration of cells and areas of focal, recent necrosis. There was mild gliosis of the anterior horns and lateral columns of the spinal cord. The cerebral white matter revealed mild spongiosis and gliosis. The cerebral cortex was well preserved, with occasional misplaced neurons. The cerebellar cortex demonstrated some maturation delay and focal Purkinje cell loss. No inflammatory cells were observed in the any of the areas described.

Discussion

Möbius syndrome is a neurologic disorder characterized by cranial nerve paralysis, usually involving the facial (VII) and abducens (VI) nerves [1]. The paralysis is usually bilateral, and other cranial nerves can be involved. Various craniofacial, musculoskeletal, and cardiac malformations, as well as mental retardation, may be associated, giving rise to the term Möbius-like syndrome [1]. Because of the ophthalmologic findings, many patients are diagnosed and treated by ophthalmologists. The infant in this report is similar to previously reported patients in terms of the location of the lesion, involvement of cranial nerve nuclei VI and VII, and in the pathology observed in these

Figure 1. Histologic (light microscopic) sections from normal infant brain (A) and brain from the infant with expanded Möbius syndrome (B). The illustrations are microscopic images of brain tissue from the brainstem, demonstrating the difference in the number of cells and cell types between a normal brain and the current patient. (A) Section through the caudal midbrain reveals the normal clustering of neuron cell bodies (●) and small myelinated axon (arrow). In addition to the normal large neurons, small glial cells can be seen (○). The cells are arranged in a normal density within the brain parenchyma (original magnification $\times 25$). (B) Section through the caudal midbrain from the infant with Möbius syndrome. Notably absent are the clusters of large neurons, with only a single neuron present in the photograph (●). The axon tracts are no longer apparent. In addition, a marked increase in the density of the small glial cells in the parenchyma is apparent. This hypercellular background is distinctive of a diffuse gliosis (original magnification $\times 25$).
lesions, namely gliosis and loss of neurons. The unique feature in this patient is the extensive involvement of various cranial nerve nuclei and areas of the brainstem without other malformations. The additional brain areas involved in this patient are predictable based on their increasing sensitivity to hypoxic/ischemic injury. Although the extent of the injury and the numerous clinical features described in this patient are more than those described in other patients with Möbius syndrome, the described clinical features in this patient are indeed consistent with a larger-than-usual lesion. Occasionally, reported patients have been described with Möbius syndrome even though they do not possess all of the required features. Perhaps this spectrum of clinical features required to apply the diagnosis of Möbius syndrome reflects the uncertainty of the etiology of this disorder.

The exact etiology of Möbius syndrome is unknown. Different schemas of etiologies have been proposed in an attempt to understand the pathogenesis of this disorder. These categories are summarized as follows [2]: (1) aplasia or hypoplasia of cranial nerve nuclei; (2) cranial nerve nuclei destruction; (3) peripheral nerve abnormalities; and (4) primary myopathies. Because of the wide range of clinical expression of this disease entity, it has been proposed that the Möbius syndrome and its variants may be the result of an hypoxic/ischemic event [3]. Aplasia or hypoplasia resulting from hypoxic damage is proposed to have two possible etiologies. The first is vascular insufficiency secondary to an interruption of blood flow from the compression of fetal vessels near the developing cranial nerve nuclei VI and VII [4]. Multiple causes of the interruption of blood flow are proposed [4], including trauma, placental abruption, and others. The second possible etiology is an anomaly of cerebral circulation development [5]. A decrease in blood flow during a critical time of development can result in an hypoxic/ischemic lesion, which leads to Möbius syndrome. Both of these etiologies can account for the concurrent skeletal anomalies observed in some patients.

Familial transmission has been reported in 27 patients [6]. Interestingly, recurrence risk is very low if there are associated skeletal defects [5]. In one family with autosomal-dominant Möbius syndrome, a gene was localized to chromosome 3q by linkage analysis [7].

Neuropathologic studies of Möbius syndrome patients have demonstrated brainstem atrophy and/or necrosis, along with other occasional brain malformations. Histologic examination reveals gliosis and mineralization with loss of neurons, especially in the area of the affected cranial nerve nuclei [2,8]. The extent of injury observed in an individual patient would be dependent on the timing and the severity of a particular insult. Ischemia has been proven to result in calcifications and necrosis of cranial nerve nuclei, which are characteristic of Möbius syndrome [3]. Hypoxic-ischemia might explain the diffuse nature of the extensive gliosis and mineralization viewed in our patient.

One of the interesting features of the present patient was the intermittent repetitive jerky arm movements noted in utero. Prenatal seizures have been described [9]. Although review of the recorded sonogram raised the possibility of focal convulsions, this is unlikely because seizure activity is not a characteristic of Möbius syndrome.

The outstanding feature of this patient is the extent of the pathology. Involvement included cranial nerves III-XI, midbrain, brainstem, and parts of the spinal cord, explaining the patient’s course. Although there may be disagreement as to the diagnosis of Möbius syndrome, the location of the pathology in the brain and the clinical features are like those in others described in the literature. We have no definitive explanation for the tremor of the left arm and the hypertonicity that the patient presented with as a fetus. We can speculate that the ongoing gliosis, resulting from the unknown etiology of this pathology, interfered with developmental events in either motor areas of the brain or spinal cord, resulting in the tremor and hypertonicity.
References


CONNECTIONS—Web Site Update
Provided by Steven M. Leber, M.D., Ph.D. and Kenneth J. Mack, M.D., Ph.D.

Recently the Child Neurology Society has moved its website to www.childneurologysociety.org. The Child Neurology Foundation, a newly formed foundation whose purpose is to advance research and educational efforts in child neurology, can be found at www.ChildNeurologyFoundation.org.