Athabascan Brainstem Dysgenesis Syndrome

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We report a new disorder with diverse neurological problems resulting from abnormal brainstem function. Consistent features of this disorder, which we propose should be called the Atabascan brainstem dysgenesis syndrome, include horizontal gaze palsy, sensorineural deafness, central hypoventilation, and developmental delay. Other features seen in some patients include swallowing dysfunction, vocal cord paralysis, facial paresis, seizures, and cardiac outflow tract anomalies. All affected children described are of Athabascan Indian heritage, with eight children from the Navajo tribe and two patients who are of Apache background. The disorder can be distinguished from the Moebius syndrome by the pattern of central nervous system findings, especially the sensorineural deafness, horizontal gaze palsy, and central hypoventilation. Recognition of children with some features of Athabascan brainstem dysgenesis syndrome should prompt investigation for other related abnormalities. Published 2003 Wiley-Liss, Inc.[†]

KEY WORDS: native Americans; brainstem dysgenesis; Moebius syndrome; central hypoventilation; horizontal gaze palsy; deafness; genetics

INTRODUCTION

Central nervous system abnormalities are a common feature of many genetic disorders, but few of these are associated with dysfunction at the level of the brainstem. The most common congenital brainstem disorder is the Moebius syndrome. Moebius syndrome is primarily a disorder of cranial nerve paralyses and is usually sporadic and without deafness or mental retardation, although severe cases may be developmentally delayed. It shows no ethnic predilection [Gorlin et al., 2001].

We report on ten Athabascan Indian children with an apparently heritable disorder of brainstem dysfunction. Several patients were previously described in abstracts at academic meetings [Friedman et al., 1996, 1997; Erickson, 1999]. This disorder was called "Navajo brainstem syndrome" and assigned OMIM # 601536. We provide the first complete account of this disease and believe given the wider ethnic distribution that a better description is "Athabascan brainstem dysgenesis."

The syndrome has some features that overlap with the Moebius syndrome but is clinically distinct in having sensorineural deafness, horizontal gaze palsy, central hypoventilation, and severe developmental delay as consistent features. Both the cause and the mode of inheritance of this disorder are currently unknown, although its occurrence within a genetically isolated population, recurrence within two sibships, and equal sex distribution suggest autosomal recessive inheritance. The purpose of this report is to provide a full clinical description of this unique disorder and to suggest diagnostic criteria that will aid in its identification within American Indian and other population groups.

CLINICAL REPORTS

Three case reports below illustrate the clinical spectrum of this disorder.

Patient 1

Patient 1 was a 36-week 2,854 g Navajo female born to a 22-year-old gravida 3 para 2 female by normal spontaneous vaginal delivery with Apgars of 8 at 1 min and 9 at 5 min. At 3 weeks of age, the patient had an upper respiratory infection and developed stridor with

respiratory distress. Evaluation demonstrated bilateral vocal cord paresis, dysfunctional swallowing, and aspiration. She had decreased facial movement and absent lateral gaze. Brainstem auditory evoked response (BAER) showed severe sensorineural hearing loss, and cold caloric testing showed no response. Echocardiogram revealed a trivial patent ductus arteriosus. A magnetic resonance image (MRI) of the head including the brainstem was read as normal. She was given a diagnosis of "Moebius syndrome variant." Tracheostomy and gastrostomy were placed because of the risk of recurrent aspiration with her vocal cord paresis.

At 6 months of age, she was noted to have a persistent compensated respiratory acidosis. While awake on room air she had an arterial blood gas of pH 7.44, pCO_2 of 53, PaO_2 of 66, and base excess of +9. With the patient asleep the pCO_2 increased to 76 torr and PaO_2 decreased to 54 torr. No obstructive or central apnea was noted during a sleep study. Night-time mechanical ventilation was begun. At 3 years of age, she began to have generalized tonic clonic seizures which were well controlled with carbemazepine. By age 5 years, her respiratory drive had improved. She was weaned from night-time mechanical ventilation. She began aminophylline and with a serum level of 11 µg/ml she had normocarbia while awake and asleep, and mild hypoxemia only while asleep. The night-time hypoxemia was treated successfully with a 30% oxygen tracheostomy collar. Swallowing and vocal paresis also improved sufficiently so that she began to feed by mouth and had her gastrostomy tube removed. At age 8 years, a neuroophthalmologic examination demonstrated the gaze paresis to be a horizontal gaze palsy rather than a sixth nerve palsy.

Achievement of major motor milestones was severely delayed. The child sat unassisted at 17 months and walked independently at 4 years with a wide-based and unsteady gait. At age 11 years, psychometric evaluation showed severe intellectual impairment. The Callier–Azusa Scale showed a cognition and communication score of 8 months and a social development score of 18 months. The Bayley Scales of Infant Development showed a mental developmental age of 12 months and a motor developmental age of 36 months.

She continued to be clinically stable and at 10 years of age the patient's tracheostomy site was closed. She remained on aminophylline but refused to wear an oxygen nasal canula during sleep. Over the next 2 years, she had increasing hypoxemia and respiratory acidosis. While awake, oxygen saturation would be in the 85% range but while asleep would decrease to as low as 50%. She had increasing daytime lethargy. She developed polycythemia with the hematocrit increasing to 73%. She required therapeutic phlebotomy. In hopes of decreasing her airway resistance and improving her oxygenation and ventilation she had a new tracheostomy placed but post-operatively suffered a catastrophic bilateral vertebral artery stroke. No coagulopathy was identified. She was discontinued from life support. The family declined an autopsy.

Of note is that a previous sibling had died at age 3 months. He had had several episodes of pneumonia and then was found dead unexpectedly at home. His death certificate was signed as sudden infant death syndrome though no autopsy had been performed.

Patient 2

Patient 2 was a term 3,720 g infant born to a 23-year-old gravida 3 para 2 female by cesarean section for failure to progress with Apgars of 5 at 1 min and 6 at 5 min. He had a mild right facial paresis noted at birth.

At 2 weeks of age he had cough, noisy breathing, and spitting up. He was hospitalized with aspiration pneumonia that was treated with anti-reflux measures. At 3 months of age, he presented with respiratory acidosis requiring intubation and mechanical ventilation. An echocardiogram showed pulmonary hypertension and right ventricular hypertrophy. These findings were felt secondary to hypoxia as they resolved in 5 days with mechanical ventilation. He was also noted to have a bicuspid aortic valve. He was weaned from the ventilator but found to have a persistent, compensated respiratory acidosis. While awake, an arterial blood gas showed a pH of 7.38, pCO_2 of 58, pO_2 of 58, and a base excess of +7. A polysomnogram showed no obstructive or central apnea, but while asleep his oxygen saturation decreased to 54% and his pCO_2 increased to 64 torr. He begun on aminophylline and his respiratory acidosis resolved and his oxygen saturation was 100% while on oxygen by nasal canula. He was initially described as having "atypical Moebius syndrome." Further evaluation demonstrated a horizontal gaze palsy. He was shown to have sensorineural deafness and no response to cold caloric testing. He had a normal MRI of the brain and brainstem and a normal electroencephalogram. Bronchoscopy showed bilateral vocal cord paresis and findings consistent with aspiration. He underwent gastrostomy placement for tube feeding.

He made steady improvement over the next few years. By 3 years of age, he had improved respiratory drive. He had a normal sleep study and normal oxygen and pCO_2 values while on aminophylline. He discontinued his night-time oxygen. At 5 years of age, his swallowing had improved. He began oral feeding and his gastrostomy tube was removed. By 11 years of age, he was able to feed and dress himself. He could walk without assistance though his gait is wide based. He attended a school for the deaf but was able to learn only ten signs. The Leiter International Performance scale, which assesses nonverbal intelligence, showed an IQ score of 43 consistent with moderate to severe mental retardation.

Patient 5

Patient 5 was a term 3,170 g Navajo female born to a 23-year-old gravida 2 para 3 female by normal spontaneous vaginal delivery with Apgars of 9 at 1 min and 10 at 5 min. She was the sibling of patient 4 in Table I who was already known to have had Athabascan brainstem dysgenesis syndrome. Family history was consanguineous with parents sharing common great grandparents.

She presented at 1 month of age with congestive heart failure secondary to critical coarctation of the

TABLE I. Clinical and Laboratory Features of Patients With Athabascan Brainstem Syndrome

Patient number and ethnicity	Horizontal gaze palsy	Developmental delay	Sensorineural deafness	Central hypoventilation	Cold caloric testing	Facial paresis	Cardiac anomaly	Seizure disorder	Vocal cord paresis
Navajo	+	+	+	+	NR	Bilateral	Patent ductus arteriosus	+	+
Navajo	+	+	+	+	NR	—	Bicuspid aortic value	—	+
Navajo	+	+	+	+	NR	Unilateral	—	—	—
Navajo	+	+	+	+	NR	Bilateral	—	—	—
Navajo	+	+	+	+	NR	Bilateral	Coarctation of aorta	+	—
Navajo	+	+	+	+	NR	—	Double aortic arch	—	—
Navajo	+	+	+	+	ND	—	Tetrology of Fallot	+	—
Navajo	+	+	+	+	ND	Bilateral	—	+	—
Apache	+	+	+	+	ND	—	Aortic valve stenosis	—	—
Apache	+	+	+	+	ND	Bilateral	Aberrant L. subclavian artery	—	—
Total	10/10	10/10	10/10	10/10	6/6	6/10	7/10	4/10	2/10

NR, non-reactive; +, finding present; ND, not done; −, finding not present.

descending thoracic aorta. Her cardiac defect was successfully repaired and because of her affected sibling she underwent evaluation for other features of Athabascan Brainstem Dysgenesis Syndrome. She was confirmed to have a horizontal gaze palsy. BAER showed sensorineural hearing loss, and cold caloric testing showed no response. She had decreased tone and decreased facial movements. Bronchoscopy showed normal vocal cord function. A MRI of the brain and brainstem was normal. An electroencephalogram showed mild posterior generalized slowing but no epileptiform activity. A sleep study showed no obstructive or central apnea but marked hypoventilation. Awake pulse oximetry showed an oxygen saturation of 88% but while asleep the oxygen saturation was as low as 55% and her pCO_2 was 62 torr. With the addition of aminophylline to achieve a serum level of 12 μg/ml and supplemental oxygen of 0.5 L/min she had oxygen saturation of 100% and normal pCO_2 awake and asleep.

At 6 months of age, she had recurrent pneumonia with respiratory failure requiring intubation and mechanical ventilation. A repeat bronchoscopy again found normal vocal cord function but now showed elevated index of lipid laden macrophages diagnostic for aspiration. This finding and the history of recurrent pneumonia were felt to be consistent with aspiration and she underwent gastrostomy placement for tube feedings.

Developmental evaluation at 6 months of age showed delay. She could neither sit nor roll. She could grab objects but could not transfer. She could fix on objects but not follow.

At 7 months of age, she presented in septic shock with pneumococcal meningitis and died. Parents declined an autopsy.

A summary of clinical and laboratory features of the ten patients with Athabascan brainstem dysgenesis syndrome are listed in Table I. Evaluation to identify a potential etiology for this disorder was negative: five patients had normal tests for organic and amino acid disorders and six patients had high resolution chromosome studies that were normal. No prenatal toxins or medication exposures were identified. No autopsy data is available, as such studies are not consistent with Navajo cultural practices.

All patients had sensorineural deafness, horizontal gaze palsy, central hypoventilation, and developmental delay. The sensorineural deafness was confirmed by BAER and 6/6 evaluated also had no response to cold caloric testing.

The horizontal gaze palsy was most remarkable in its difference from a pure sixth nerve palsy. Like the sixth nerve palsy there is no lateral eye movement but in this particular gaze palsy there is neither lateral nor medial eye movement on attempted horizontal gaze. Medial eye movement is present, however, during convergent gaze.

Central hypoventilation was found in all patients but varied in severity. One child, patient 6, remained ventilator dependent until death at age 8 years of chronic lung disease. A second patient, patient 1, required night-time mechanical ventilation until 3 years of age when she weaned to supplemental oxygen by tracheostomy collar. Oral aminophylline and night-time

supplemental oxygen was satisfactory treatment for the other eight patients when they were infants. For all patients the degree of hypoventilation was more severe while asleep and in some hypoventilation was only present during sleep. Respiratory drive improved in all patients with age and only patients 1 and 6 required night-time oxygen after age 5 years.

Developmental delay was present in all patients and varied from moderate to severe. The two patients who were ventilator dependent, patients 1 and 6, had the greatest impairment. Both children showed development functioning at an infant level, raising the possibility of greater disability secondary to hypoxic brain injury. The two ventilator dependent patients were also two of the four children with seizure disorders raising the issue of whether the seizures reflected more severe global brain disease or were secondary to hypoxic injury. Other patients that survived to childhood learned to feed and dress themselves and had nonverbal IQ in the 40–60 range. The two highest functioning children learned over 100 signs in American Sign Language.

Neurologic examination of older patients demonstrated all had an unsteady, wide based gait and dysmetria on reaching for objects suggestive of cerebellar dysfunction. Patients had normal strength and reflexes without hypotonia or spasticity. Magnetic resonance imaging of the brainstem was normal in 9/9 examinations with no evidence of hypoplasia, atrophy, or calcifications. Cerebral imaging was normal in all except patients 1 and 6, the two patients who were ventilator dependent. These patients had cerebral atrophy that was felt secondary to recurrent hypoxic injury.

Only 2/10 children had vocal cord paresis but 6/10 children had swallowing dysfunction and recurrent aspiration as infants severe enough to require gastrostomy tube placement for feeding. Vocal cord paresis and swallowing dysfunction were confirmed by bronchoscopy to have resolved in all patients by age 3 years and all eventually fed by mouth.

Lastly, 6/10 patients had facial nerve paresis, a finding seen in Moebius syndrome. However, 7/10 patients had a structural cardiac defect, a feature not typically associated with the Moebius syndrome. The anomalies were of various types but all involved defects of the cardiac outflow tract.

DISCUSSION

The ten children described in this article have a unique disorder of horizontal gaze palsy, central hypoventilation, sensorineural deafness, and severe developmental delay. These are features that serve to distinguish this disorder from the Moebius syndrome, though the two conditions share some common features.

Many of the patients in this report were initially diagnosed with Moebius syndrome because of their gaze palsy. However, closer scrutiny has shown that patients with Athabascan brainstem dysgenesis syndrome have a horizontal gaze palsy rather than a pure sixth nerve palsy as seen in Moebius syndrome. The horizontal gaze palsy is manifested as a lack of conjugate gaze, with neither lateral movement nor medial movement on attempted horizontal gaze but with medial eye movement during convergent gaze. The origin of these ocular abnormalities is not completely delineated but appears to result from an abnormal abducens nucleus. This nucleus is located in the pons and controls two separate groups of neurons: the abducens motor neurons that project to the ipsilateral lateral rectus muscle, and the internuclear neurons that join the contralateral medial longitudinal fasciculus and project to the contralateral medial rectus neurons to control medial gaze of the contralateral eye.

A second clinical feature, which led to the erroneous diagnosis of Moebius syndrome, was the facial diplegia, which was seen in 6/10 of our patients. However, swallowing dysfunction, recurrent aspiration, and vocal cord paresis, reflecting dysfunction of cranial nerves IX, X, and XII were common in our patients but are found rarely in Moebius syndrome cases [Carr et al., 1997]. Furthermore, sensorineural hearing loss is generally not encountered in Moebius syndrome while it was a finding in all patients. Lastly, developmental delay of a moderate to severe nature was seen in all the patients in this report but is found in fewer than 10% of Moebius patients [Gorlin et al., 2001].

A particularly unique feature of Athabascan brainstem dysgenesis syndrome is the central hypoventilation. Central hypoventilation [Fujita et al., 1991; Igarashi et al., 1997] and sleep-disordered breathing [Gilmore et al., 1991], are rarely described in association with Moebius syndrome. Although the pathogenesis is not known with certainty, central hypoventilation is believed to be the result of dysfunction of chemoreceptors in the respiratory control centers of the brainstem [Beckerman et al., 1986]. Two investigators have identified patients with congenital central hypoventilation and cranial nerve defects though these patients do not match the constellation of findings seen in our report. Khalifa et al. [1988] described twin girls with central hypoventilation and abnormal swallowing. Another paper described siblings with central hypoventilation, ophthalmologic abnormalities, hypotonia, vocal cord paralysis, and cerebral atrophy [Weese-Mayer et al., 1992].

Lastly, the cardiac outflow tract anomalies seen in 7/10 patients is particularly intriguing. Cardiac defects are not felt to be part of the Moebius syndrome but embryonic disruption of the subclavian and vertebral artery blood supply has been hypothesized as the etiology for Moebius syndrome, oral-limb deficiency syndrome, and Poland Syndrome [Bavnick and Weaver, 1986; St. Charles et al., 1993]. Is Athabascan brainstem dysgenesis syndrome the result of a prenatal vascular disruption of which the cardiac outflow defects are evidence? The unexpected fatal basilar artery stroke of patient 1 also raises the possibility of an undiagnosed vascular anomaly.

In this regards, there is an interesting case report from 15 years ago from University of New Mexico. They described a Native American infant with transposition of the great vessels, facial weakness, sixth nerve palsy, absent cold caloric response, and an absent left hand. Hearing was not tested nor was respiratory drive

described. The patient died at 3 months following heart surgery and autopsy was not performed. The authors speculated that the combination of cardiac defect, limb defect, and cranial nerve deficiencies could be explained by vascular disruption in the fourth to sixth week of gestation [Raroque et al., 1988]. It is likely this patient was an Athabascan Indian and had the syndrome we now describe.

The apparent ethnic predilection of this disorder may represent a founder effect in the Navajo and Apache tribes. Historical data show that both the Apache and Navajo tribes underwent a severe genetic bottleneck in the late 19th century during armed conflict with the United States Army [Holve et al., 2001]. The Navajo and Apache are known from linguistic and mitochondrial evidence to share common ancestry as Athabascan tribes [Greenberg et al., 1986; Torroni et al., 1993], which may explain the presence of this syndrome in the two patients who are of Apache background. The founder effect hypothesis is supported by the finding that severe combined immunodeficiency syndrome with a unique genotype, is found at high frequency among both the Navajo and Apache [Li et al., 1998]. Within the Navajo tribe the incidence of Athabascan brainstem dysgenesis syndrome is estimated at 1/3,000 live births [Navajo Area Indian Health Service, 1997].

The presence of this disorder in genetically isolated populations, its equal sex distribution, and the presence of the disorder within a consanguineous family all are supportive of an autosomal recessive inheritance. This is further supported by the definite recurrence in one sibship (patients 4 and 5) and the likely recurrence in another (patient 1 and her sib who died at 3 months of age prior to recognition of this syndrome). Work is currently underway to identify candidate genes for this disorder. A recent report localized a familial horizontal gaze palsy with scoliosis to #11q23-25 [Pieh et al., 2002] and this region may bear scrutiny.

In addition, it is possible that unknown environmental factors may play a role in the expression of this disorder. Use of the abortifacient, misoprostol, has recently been implicated as a cause of Moebius syndrome [Pastuszak et al., 1998]. However, no common prenatal exposures were identified in our patients.

Given the frequency of this disorder in Athabascan Indians, the presence of one finding such as sensorineural deafness or cardiac outflow defect should prompt investigation for other features of this syndrome. Recurrent aspiration pneumonia was a presentation of several patients in infancy and also should raise the possibility of this syndrome.

To make the diagnosis of Athabascan brainstem dysgenesis syndrome we suggest the following criteria: (1) sensorineural deafness demonstrated by BAER; (2) horizontal gaze palsy as shown by lack of conjugate lateral gaze but intact medial gaze on convergence; (3) Central hypoventilation awake or asleep as demonstrated by hypoxia or respiratory acidosis in the absence of underlying lung or neuromuscular disease; (4) developmental delay; and (5) one out of the four following findings; facial paresis, vocal cord paresis, seizure disorder, or cardiac outflow tract anomaly.

Lastly, general pediatricians and geneticists need to be aware of this syndrome. This syndrome may be present in sporadic cases in other ethnic groups. More importantly, an increasing number of Native Americans are moving off reservations to urban areas and will seek medical care in these settings. Early identification of these patients will be medically beneficial and will be especially important for developmental outcome. Early intervention programs with sign language may improve the severe communication deficits seen in these patients.

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