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A Case of Athabaskan Brainstem Dysgenesis Syndrome and RSV Respiratory Failure

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Abstract

Athabaskan Brainstem Dysgenesis Syndrome (ABDS) is a nonlethal, homozygous *HOXA1* mutation typically marked by central hypoventilation, sensorineural deafness, horizontal gaze palsy, and developmental delay. In this report, we present a case of a 27-month-old Navajo female with a new diagnosis of ABDS after multiple failed attempts at extubation following anesthesia in the setting of respiratory syncytial virus (RSV) bronchiolitis. Her case is significant because she lacks sensorineural hearing loss, a defining feature of previously documented cases thereby underscoring the challenges of diagnosing this disease. This case expands the ever-growing spectrum of homozygous *HOXA1* mutations and demonstrates unique junctions for diagnosis of ABDS in the critical care setting in patients lacking key features of the disease.

Keywords
Athabaskan brainstem dysgenesis syndrome, respiratory failure, HOXA1, mutation, hypoventilation, sensorineural deafness, developmental delay, respiratory syncytial virus, RSV, ABDS

Introduction

Athabaskan Brainstem Dysgenesis Syndrome (ABDS) is an autosomal recessive, nonlethal, homozygous *HOXA1* mutation. Though globally rare, incidence in Southwest Athabaskan (Navajo and Apache) populations spans 1/1000 to 1/3000 births (1)(2). This can be compared to Congenital Central Hypoventilation Syndrome (CCHS) with an estimated incidence of 1/200,000 births worldwide (3) ABDS is marked by central hypoventilation, sensorineural deafness, horizontal gaze palsy, and developmental delay (2). Other features include cardiac outflow tract anomalies, swallowing dysfunction, vocal cord paralysis, facial paresis, seizures, hypotonia, and

cerebrovascular maldevelopment (4)(5). Affected individuals span a broad spectrum with many asymptomatic cases. Similar syndromes include Moebius syndrome and Bosley-Salih-Alorainy Syndrome, though both lack central hypoventilation (5). Central hypoventilation in children should include consideration for primary neuromuscular, lung, or cardiac disease, along with brainstem lesions, CCHS, asphyxia, infection, trauma, tumor, and infarction (6). As more Athabaskan individuals leave reservations, medical professionals must gain familiarity with the spectrum of *HOXA1* mutations to prevent avoidable complications and expedite appropriate therapies.

We present a 27-month-old Navajo female with a new diagnosis of ABDS after several failed attempts at extubation following anesthesia in the setting of respiratory syncytial virus (RSV) bronchiolitis.

Case Description

A 27-month-old Navajo female with global developmental delay, patent ductus arteriosus (PDA), and sleep apnea presented with an acute, febrile respiratory illness confirmed as RSV bronchiolitis. She was admitted to a rural hospital for supportive care including supplemental oxygen and methylprednisolone.

Birth and developmental history were significant for transient poor feeding, poor visual tracking since birth, three failed newborn hearing exams with a subsequent pass, and global developmental delay, evidenced by inability to ambulate independently or speak more than two words.

At the rural hospital, persistent hypoxemia prompted a cardiac evaluation with echocardiography that revealed left ventricular hypertrophy, a tortuous aortic arch with moderate obstruction, and a small PDA with left-to-right shunting. Considering these findings, she was transferred to a tertiary pediatric hospital for further workup and management.

On the pediatric floor, blood gas analyses showed hypercarbia with metabolic compensation, suspicious for chronic hypoventilation. She consistently demonstrated generalized hypotonia and inconsistent tracking, specifically restricted lateral eye movements. Persistent hypoxemia and abnormal echocardiogram prompted further cardiac evaluation. On hospital day (HD) 3, a cardiac CT under general endotracheal anesthesia confirmed coarctation of the aorta and hypoplastic transverse arch. She was unable to be extubated due to persistent hypoxia and hypercarbia and was transferred to the cardiovascular intensive care unit.

Extubation attempts were initially deferred due to *Moraxella* tracheitis, treated with antibiotics and airway clearance. She weaned ventilator settings and was extubated to non-invasive support with bilevel positive airway pressure (BiPAP) on HD7. Within hours, she developed hypercarbia due to hypoventilation with a blood pH of 6.98 requiring reintubation.
Persistent central hypoventilation, hypercarbia, and cardiac outflow tract anomaly prompted investigation for ABDS. Brain MRI showed diffuse parenchymal volume loss with no brainstem abnormalities. Brainstem Auditory Evoked Response (BAER) testing showed no evidence of sensorineural hearing loss. Chromosome microarray testing confirmed homozygous *HOXA1* mutation, consistent with ABDS.

Ventilator settings were again weaned, caffeine therapy initiated, and sedation medications discontinued for several days to avoid exacerbation of central hypoventilation. Unfortunately, repeat extubation failed due to

stridor and hypoventilation, so she was reintubated and underwent an airway evaluation that revealed posterior vocal fold granulomas, which were debrided.

On HD33, the patient was successfully extubated to BiPAP. She weaned to room air during the day and BiPAP at night which she continued after discharge on HD57.

Discussion

In the critical care setting, familiarity with ABDS is important because patients can present with severe symptomatology out of proportion to their underlying disease. Minor respiratory illnesses or anesthesia can greatly exacerbate central hypoventilation and potentially lead to prolonged endotracheal intubation, mechanical ventilation, and associated complications such as ventilator-associated pneumonia, airway trauma, and habituation to sedation medications (2). Patients like this, who lack certain key features of ABDS—namely sensorineural deafness—are particularly challenging since diagnosis can be delayed (2). This case further illuminates the spectrum of homozygous *HOXA1* mutations and emphasizes the importance of maintaining a high index of suspicion for ABDS in Athabaskan patients to anticipate the illness course and provide tailored medical care.

Conclusion

Overall, as Athabaskan individuals spread geographically, this case underscores the importance of widespread familiarity with ABDS for physicians. Basic knowledge of the features of ABDS will help identify individuals who may present with events such as infection or anesthesia that unmask an underlying abnormality, and their care can be directed at the unique challenges they present.

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