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Rare Occurrence DNAJB4 Gene Mutation Leads to Early Respiratory Failure in an Indian Neonate

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ABSTRACT

DNAJ/HSP40 co-chaperones are integral to the chaperone network, bind client proteins, and recruit them to HSP70 for folding. DNAJB4 belongs to the evolutionarily conserved DNAJ/HSP40 protein family. Northern blot analysis detected its high expression in skeletal muscle, heart and pancreas and lower expression in the brain, placenta and liver. Loss of function mutation of the DNAJB4 gene can lead to hereditary myopathy and early respiratory failure. Clinical description: A 13-day-old neonate at vaginally delivered term gestation was admitted with us with a history of meconium aspiration requiring respiratory support and neonatal seizure. In 75 days of NICU stay, the patient required invasive ventilatory support on most days with five extubation failures throughout the stay. To rule out causes of prolonged mechanical ventilation neonate was investigated with basic blood investigations and radiological scans. MRI of the brain and spine turned out to be normal. Apart from antibiotics-responsive hospital-acquired infection, the neonate's blood investigations were normal. To diagnose the genetic possibility whole EXOME sequencing was done turns out to be positive for a heterozygous mutation in the DNAJB4 gene. Management and outcome: The patient received critical neonatal care with invasive respiratory support and later on had a tracheostomy. Hospital-acquired sepsis was treated with intravenous antibiotics. Intermittent five extubation trials were given. The patient expired on the 79th day of life with respiratory failure. This case highlights the infrequent genetic cause of early respiratory failure with prolonged ventilation in the neonatal age group, as respiratory and cardiac causes are usually more common among them.

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Key Words
Respiratory failure, DNAJB4, HSP70

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INTRODUCTION

Clinical description: A full-term male neonate, born out of nonconsanguineous marriage, first in birth order, delivered by vaginal delivery, cried immediately after birth, liquor was meconium stained and was referred to us on the 13th day of life with meconium aspiration syndrome requiring mechanical ventilation with history of three failed extubation trial at referring NICU. In antenatal history, the mother was on regular follow-ups with all antenatal scans being normal, liquor was adequate fetal movements were well perceived and there was no history of antenatal illness. Mother had a history of seizures which were well controlled on levetiracetam with no episodes throughout pregnancy. On examination, heart rate was 132/min, respiratory rate was 46/min and maintaining saturation on ventilatory support. The baby's birth weight was 3.3kg, head circumference was 33 cm and length was 49 cm, all being appropriate for his gestational age. After receiving at our set-up, we kept the baby on HFOV (high-frequency oscillatory ventilation) given the clinical condition following meconium aspiration syndrome. 2D echo findings were suggestive of PPHN (persistent pulmonary hypertension of the newborn), after having the cardiologist advise injection sildenafil was started. After providing HFOV ventilation for 2 days as fio2 requirement decreased Baby was weaned off to PTV (pressure targeted ventilation) and an extubation trial was given on the 24th day of life, with tolerating intermittent tachypnea and distress, CPAP continued for 6 days, but as there were signs of impending respiratory failure and blood gas suggestive of respiratory acidosis on 30th day of life. Following this until the patient succumbed on the 79th day of life, four more extubation failures occurred, on the 69th day of life, the patient required a tracheostomy considering prolonged mechanical ventilation. The patient required intravenous antibiotics during a hospital stay on culture-proven hospital-acquired sepsis. Blood investigations on receiving were done. CBC showed hemoglobin: 13.2 gm/dl, total counts: 15660/mm3, differential counts: neutrophils: 65% lymphocytes:21%, platelet counts: 2.05lacs. Renal function tests were normal. Given the prolonged ventilatory requirement even after addressing individual management of meconium aspiration syndrome and PPHN, we have decided to investigate other structural, neurological and genetic causes for this. Considering neurological causes that possibly involve the respiratory center in the brain and/or upper spinal cord abnormalities causing respiratory failure and frequent failures at extubations CT and MRI brain and spine were planned and turned out to be normal. Suspecting another differential of any upper airway structural and/or vascular lesions that can lead to extubation failures and persistent ventilatory requirement. For that, virtual as well as physical bronchoscopy by an expert pediatrics surgeon showed no significant abnormal findings. Considering the involvement of lung vasculature and/or structural lung abnormalities like cystic malformations or pulmonary hypoplasia, CT lung with pulmonary angiography was planned, which showed changes of Pulmonary arterial hypertension in vasculature and the rest findings were normal. Meconium aspiration syndrome itself can be the cause of prolonged ventilation. However, that cause is well excluded in radiological investigations. Considering rare genetic causes for persistent respiratory failures whole EXOME analysis was planned, which turned out to be positive for DNAJB4 gene heterozygous mutation located at exon 2, variant nomenclature c.676-707delinsGT located at chromosome 1p31.1.

Management and Outcome: The patient was managed in the neonatal intensive care unit with various modes of invasive mechanical ventilation including conventional and high-frequency ventilation. The patient was investigated with brain & spine radiological scans, virtual & physical bronchoscopy and CT lung with angiography. Hospital-acquired sepsis was managed with intravenous antibiotics. After intermittently failed extubation trials, the patient required a tracheostomy for further invasive ventilatory support. On the 79th day of life, the patient succumbed to death.

RESULTS AND DISCUSSIONS

Over 100 genes and proteins are associated with distinct neuromuscular phenotypes and pathologies. For example, some genetically defined myopathies have specific associated symptoms such as facial weakness or respiratory involvement. DNAJ/HSP40 co-chaperones are essential for chaperone-client specificity[1]. They are grouped into three main categories DNAJA, DNAJB and DNAJC based on their domain similarities. DNAJ proteins are highly conserved across species including lower eukaryotes. For example, the yeast DNAJB chaperone Sis1 is essential for yeast viability and the human DNAJB1 can complement for its absence. Dominant variants in DNAJB6 and recessive mutations in DNAJB2 cause hereditary myopathy and neuropathy, respectively. DNAJB chaperones recognize misfolded client proteins and recruit HSP70 proteins[2]. The DNAJB-client complex stimulates HSP70 ATP hydrolysis which then facilitates the refolding of the client 6. In the case of DNAJB6, it recognizes Z-disc proteins and recruits HSP70. Dominant mutations in DNAJB6 trap HSP70 at the Z-disc resulting in an HSP70-dependent gain of function. DNAJB4 gene which is located at the short arm of chromosome 1, similar to DNAJB6 is essential

for myofibril maintenance and that aberrant chaperone function leads to isolated muscle disease[3-5].

As in our case a full-term male neonate, born out of nonconsanguineous marriage, first in birth order, delivered by vaginal delivery, cried immediately after birth, liquor was meconium stained and was referred to us on the 13th day of life with meconium aspiration syndrome requiring mechanical ventilation with history of three failed extubation trial at referring NICU. We offered invasive mechanical ventilation with conventional and high-frequency modes of ventilation with intermittent five failed trials of extubations and the requirement of tracheostomy. For a hospital-acquired infection, a neonate requires intravenous antibiotics. Considering prolonged mechanical ventilation and failed extuabtions other differentials of that excluded. Tracheomalacia and other probable causes of upper airway obstructions can lead to this, which were excluded on virtual and physical bronchoscopy[6]. Any structural brain and spinal cord abnormalities especially the upper spinal cord that manage respiration could be the cause of failed extubations, however normal brain and spinal scans excluded that[7]. Structural lung involvement like CPAM (congenital pulmonary airway malformation) was also suspected, CT lung excluded that[8]. After excluding more commoner causes, we planned genetic analysis whole EXOME, which turned out to be positive for heterozygous DNAJB4 gene mutation located at 1p31.1 chromosome. The patient required invasive mechanical ventilatory support along with critical care, though even after multiple attempts of exhumations patient succumbed on the 79th day of life. Parents were genetically counseled and advised for antenatal screening for the same in further pregnancies.

CONCLUSION

This case highlights the infrequent genetic cause of early respiratory failure with prolonged ventilation in the neonatal age group, as respiratory and cardiac causes are usually more common among them. Neonatologists and pediatricians should consider genetic causes like DNAJB4 gene mutation as one of the differentials of early respiratory failures in neonates that are not due to other common structural causes.

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