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Short Communication

Lethal Neonatal Respiratory Distress Syndrome Due to ABCA3 Mutation: Case Series from Saudi Arabia

Sameer Y Al-Abdi, Hesham J Al-Algirim, Kamal I Dabelah, Taher A Mousa, Hind M Algatam,

Department of Pediatrics, King Abdulaziz Hospital, Ministry of National Guard Hospital, Al-Ahsa, Saudi Arabia

***Corresponding author:** Sameer Y Al Abdi. Department of Pediatrics, King Abdulaziz Hospital, Ministry of National Guard Hospital, PO Box 2477, Al-Ahsa 31982, Saudi Arabia Tel: +966135339999; E-mail: AbdiS@ngha.med.sa.

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The autosomal recessive ATP-binding cassette transporter A3 (ABCA3) mutations are rare but likely the most common inherited surfactant dysfunction [1]. Its neonatal onset form manifests soon after birth as a severe respiratory distress syndrome (RDS) or respiratory failure [1]. Almost all these newborn infants die within the first three months of life as no specific therapy exist and a lung transplant is the only option extends their survival [1-4]. Anecdotally, systematic corticosteroid, hydroxychloroquine, and azithromycin have been found to be partially effective [2-5].

The ABCA3 mutations have been reported from various races and ethnic groups [1]. Effected individuals have not particular demographic characteristics except to Caucasian Middle Eastern (CME) patients have been mostly born from consanguineous marriages [1]. Three Saudi infants, from the same trip, with c.4545C>G ABCA3 mutation have been reported by others [4]. Thus, we aimed to report another five Saudi infants with three different ABCA3 mutations. Hoping this will increase awareness of ABCA3 in Saudi Arabia and stimulate registry and collaborations nationally and regionally.

From 2006 to 2015, five Saudi full term newborns infants were admitted soon after birth to our neonatal intensive care unit due to respiratory distress and were found to have three different ABCA3 mutations. These infants were born to three consanguineous parents (infant 1, 2, and 3 were siblings). Their initial chests X-rays were very similar to RDS. Their clinical presentation, investigations, managements, and outcomes are summarized in (Table 1).

Case Number	Lung CT findings (age at imaging)	Respiratory support	Surfactant	Anecdotal treatment	Lung histopathology findings	Mutation	Age of death
1* (Male)	Septal thickening and ground-glass opacity (day 19)	Conventional (CMV) and high-frequency oscillation mechanical ventilation (HFOV) dependent	2 doses	Dexamethasone	Alveolar proteinosis Desquamative interstitial pneumonia	Homozygous missense c.4648T>G (p.Luc1553Pro) in exon 30 Parents are heterozygous carriers	1month
2* (Male)	Bronchiectatic changes and air-trapping (day 20)	CMV and HFOV dependent	9 doses	Dexamethasone	Pneumocyte II hyperplasia Interstitial thickening Lobular-alveolar remodeling Small pulmonary arteries hyperplasia Electronic microscope examination was not performed		2months
3* (Male	No CT imaging	CMV and HFOV Continuous positive airway pressure Nasal cannula for 75 days	30 does (mostly as intubation-surfactant-extubation technique)	Dexamethasone Hydroxychloroquine	Lung biopsy was not performed		4months

4 (Male)	Air bronchogram, opacity, and interstitial emphysema (day 28)	CMV dependent	4 doses		Pneumocyte II hyperplasia Interstitial thickening Lobular-alveolar remodeling Small pulmonary arteries hyperplasia Lamellar dense bodies	Homozygous nonsense c.4545C>G (p.Tyr1515X) in exon 29 Parents were not tested)	2months
5 (Female)	No CT imaging	CMV and HFOV dependent	8 doses	Hydroxychloroquine	Lung biopsy was not performed	Homozygous missense c.4444 C>T(p. Arg 1482Trp) in exon 29 Parents were not tested	2months

Table 1: Characteristics of five newborn infants with ABCA3 mutation.

Mutation responsible for surfactant protein B or C was not detected by molecular testing of these infants. An open lung biopsy was performed in three infants [1,2,4] and (Table 1) depicts histopathological findings. Serial echocardiography exams were normal in infant number 4 but reveled severe pulmonary hypertension in the other four infants [1-5] at age of 1, 20, 83, and 4 days of life, respectively. Inhaled nitric oxide was used in the management of these four infants and sildenafil was only used for two infants [2-5].

Hospital course, lung histopathology finding, and outcome of these infants were similar to other reports on ABCA3 mutations [3,4]. An ABCA3 birth prevalence might be 2.0 per 10,000 live births (95% confidence interval: 1.0-4.0 per 10,000) based on our total live births 24,848from 2006 to 2015 However, national registry is needed to estimate prevalence ABCA3 mutations in Saudi Arabia.

Both our infants and CME infants with ABCA3 mutations shared one demographic characteristic that was consanguineous parents. Thus, CME infants with ABCA3 mutations are closest largest reported racial/ethnic group that our infant can be compared with. The largest cohort study to date on ABCA3 (N=185) has included the largest number of CME infants (n=36) [1].

None of our infants had compound heterozygous mutation and two infants out of previously reported 36 CME infants had compound heterozygous mutation (nonsense/misses) [1]. Homozygous misses ABCA3 mutation was identified in four of our five infants and homozygous nonsense mutation in one infant. An opposite distribution pattern of 34 homozygous mutations has been observed among CME infants with nonsense predominance. Distribution of these 34homozygous mutations were as following: 21(62%) nonsense; 10 (29%) missense;2 splice; and 1 frame shift mutation [1]. This discrepancy on distribution pattern of ABCA3 mutations between ours and CME infants might be due the small size of our cohort. Perhaps this is a genotypic characteristic of ABCA3 mutations in CME infants as misses mutation predominates in other various racial/ethnic groups [1].

Our infants were similar to CME infants regarding RDS soon after birth and death within first year of life. Thirty four (94%) of CME infants presented with RDS [1]. Of those CME infant, 32 died within the first year of life and two underwent lung replantation [1]. Two (6%) CME infant who presented at late infancy with RDS survived without lung transplantation [1].

Lung transplantation is the only available therapy to extend the survival of newborn infants with ABCA3 mutation [2]. This option was not feasible for our infants because of lung transplant experience in first years of life is limited worldwide, lacking of donors, and general and anecdotal therapy failed to stabilize them [4]. One Saudi infant with c.4545C>G ABCA3 mutation has been successfully transplanted in United States of America [4].

In summary, we reported five Saudi infants with ABCA3 mutations born at full-term to three consanguineous parents. These infants presented with severe RDS at birth and all died at < 4 months of age. Hopefully, this report will increase awareness of ABCA3 in Saudi Arabia. Given the rarity and fatality of ABCA3 mutation in newborn infants, national, global, and international collaborations and registry is urgently needed to guide clinical decision and improve the outcomes.

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