Childhood interstitial lung disease: The end of a diagnostic odyssey

Dear Editor,

Childhood interstitial lung disease is a heterogeneous group of rare disorders featuring pulmonary interstitial remodelling and diffuse parenchymal infiltrates on imaging.\(^1\) Incidence is estimated at 0.13–16.2 cases/100,000 children per year.\(^1\) *ABCA3* (ATP-Binding Cassette, Subfamily A, Member 3) (OMIM #601615) is expressed in alveolar type II cells involved in pulmonary surfactant production,\(^2\) thus attributed to surfactant metabolism dysfunction-3 (OMIM #610921).\(^3\) Differences in variant frequency and disease phenotype were reported in different ethnic groups, with Asians uniquely identified with homozygous c.4909+1G>A/c.4909+1G>A variants within an American cohort,\(^4\) whereas a Japanese cohort demonstrated 6 novel variants.\(^5\) This may result in different prognostication and outcomes. We report what is likely the first case of childhood interstitial lung disease in a Southeast Asian child with deleterious compound heterozygous *ABCA3* variants, with consideration for early genetic testing when progression is refractory to treatment.

Our patient was a term boy, born via spontaneous vertex delivery with a birth weight of 2.99kg. Antenatally, apart from an episode of maternal H1N1 infection during the 2nd trimester, there were no other complications. The father (41-year-old) and mother (35-year-old) were unrelated with no significant medical or family concerns. They had a healthy 6-year-old daughter.

The patient was born vigorous with Apgar scores of 7 and 8 at 1st and 5th minute. At 1st hour of life, he developed respiratory distress and required non-invasive ventilation (NIV). Intravenous penicillin and gentamicin were started. He was intubated by day 2. Chest X-ray showed left retrocardiac and upper lobe consolidation. Echocardiogram showed a structurally normal heart. He received 2 doses of endotracheal surfactant due to radiographic concerns for term respiratory distress syndrome (RDS), and showed transient improvement. Intravenous clarithromycin was added, and a short course of intravenous dexamethasone, oral spironolactone and hydrochlorothiazide were attempted.

He was extubated on day 9 to NIV, but required re-intubation on day 11. Blood gases showed type 2 respiratory failure. Intravenous ceftriaxone was commenced as tracheal secretion culture grew *Enterobacter cloacae*. On day 22, the third dose of surfactant was attempted as a “rescue dose”, but to no avail.

On day 26 of life, he was referred to our unit. He required high ventilatory support, with an oxygenation index of 22. Repeated chest X-ray showed diffuse bilateral ground-glass opacities (Grade IV), resembling neonatal respiratory distress syndrome. Repeated echocardiogram showed pulmonary hypertension that responded to inhaled nitric oxide. Investigations included bronchoscopy that showed no malacic airways, bronchoalveolar lavage for cytology that was negative for PAS staining, and serological blood tests that included parvovirus IgM positive and IgG negative, and negative for herpes simplex virus IgM, Epstein-Barr virus IgM, cytomegalovirus and varicella zoster IgM. High-resolution computed tomography of the thorax (non-contrasted) (Fig. 1) showed diffused ground glass changes in upper lobes and interstitial thickening; while middle and lower lobes (especially over the left side) showed consolidative changes and reduced lung volume, interlobular septal thickening and bronchial dilatations. The overall impression was extensive lung damage with fibrosis and scarring. Lung biopsy was not pursued due to significant risks of complication.

Treatments attempted included: intravenous immunoglobulin (0.4g/kg/dose for 2 days), intravenous methylprednisolone pulse therapy (20mg/kg/day, 5-day courses on a monthly basis), hydroxychloroquine (5mg/kg/day) and azithromycin (7mg/kg/dose every other day), with no sustainable improvement. Parents were not keen for tracheostomy. Lung transplantation was not feasible due to resource limitations.

Subsequent genetic testing with whole exome sequencing revealed compound heterozygous variants...
of c.3364G>A p.(Glu1122Lys) and c.737C>T p.(Pro246Leu). Both were present in the Single Nucleotide Polymorphism database (dbSNP) as rs123304338 and rs144653790, respectively. A previous study reported the c.737C>T variant together with c.1450del in an infant with neonatal respiratory distress syndrome, with the c.737C>T variant being classified as “likely pathogenic”. Although both of our variants found were reported in dbSNP, almost all of the pathogenicity prediction programmes in the VarSome platform predicted the c.737C>T and c.3364G>A variants as deleterious by 94.4% (17 out of 18 programmes) and 94.7% (18 out of 19 programmes), respectively. Therefore, both are predicted to be classified as “likely pathogenic”.

This case was consistent with neonatal respiratory failure due to surfactant deficiency. A further parental genetic study by polymerase chain reaction and sequencing of the ABCA3 gene revealed that the mother carries the c.737C>T variant whereas the father carries the c.3364G>A variant, indicating the variant was on opposite alleles, and confirming the segregation of variants. These results facilitated genetic counselling, future reproductive options, and ending the diagnostic odyssey.

Due to irrecoverable poor lung function, palliative care was pursued. At day 83 of life, the patient was extubated to high settings of bilevel positive airway pressure. Home care was untenable due to high NIV requirements. Life-sustaining support was withdrawn at 11 months old, and he succumbed peacefully.

ABCA3 variants leading to neonatal respiratory failure were mostly reported in Caucasians. The Han and Zhuang populations in Japan and China, respectively, were reported to have a carrier rate of 1.3%, lower than the US. With 2 ABCA3 variants, pulmonary phenotype varies for disease prognosis. Role of hydroxychloroquine, corticosteroids, macrolides, azathioprine, cyclophosphamide and colchicine remained uncertain. Lung transplantation was the next treatment option, but requires high expertise and facilities. The 5-year survival rate of 50% from lung transplant was not acceptable for the parents.

There are some limitations in the present study. Firstly, the association between our findings of the variants and poor prognosis requires additional cases to support the above findings. Secondly, a robust functional study is needed to prove the negative impact of these variants on the gene/protein function. Lastly, lung biopsy may still be considered to prove the variants’ pathogenicity.

To the authors’ best knowledge, this is the first reported child with likely deleterious compound heterozygous variants in Southeast Asia. Diagnosis can be made based on clinical features of RDS, imaging and genetics analysis without lung biopsy, in accordance with both European protocols and the American Thoracic Society Clinical Practice Guideline. Genetic testing can assist in prognostication, decision-making, and future family planning.

REFERENCES


Kok Joo Chan *1MBCRP, Meow-Keong Thong *3MD, Anna Marie Nathan *4MBCH, Surendran Thavagnanam *4MB, Yunsita Yakob 5MB, Chin Seng Gan 3MBBS

1 Neonatology Unit, Department of Paediatrics, University of Malaya Medical Centre, Malaysia
2 Paediatric Intensive Care Unit, Department of Paediatrics, University of Malaya Medical Centre, Malaysia
3 Genetic and Metabolism Unit, Department of Paediatrics, University of Malaya Medical Centre, Malaysia
4 Paediatric Respiratory Unit, Department of Paediatrics, University of Malaya Medical Centre, Malaysia
5 Molecular Diagnostics Unit, Specialised Diagnostic Centre, Institute for Medical Research, Malaysia

*Joint first co-authors

Correspondence: Dr Chin Seng Gan, Department of Paediatrics, University of Malaya Medical Centre, Jalan Profesor Diraja Ungku Aziz, Lembah Pantai, 59100 Kuala Lumpur, Selangor, Malaysia. Email: csgan@umm.edu.my