TWIN SISTER WITH SURFACTANT DISORDER MECHANISM DUE TO MUTATION IN *SFTPC* AT VIETNAM NATIONAL CHILDREN'S HOSPITAL

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ABSTRACT

The twin sisters were identified mutation inSFTPC, leading to a surfactant disorder mechanism, at the Vietnam National Children's Hospital. 15-month-old girls had a history of pneumonia and required ventilation when they were 3 months old, subsequently depending on oxygen support. Clinical examinations revealed chronic hypoxemia, finger clubbing, malnutrition, and the need for daily oxygen support at home. A clinical targeted genes related to childhood interstitial lung diseases was sequenced and a pathogenic missense variant c.218T>C (p.Ile73Thr) in SFTPCwas identified. Following the Delphi consensus, the patients are currently being treated with oral prednisolone, hydroxychloroquine, and azithromycin. Their mother was advised to purchase CPAP equipment for home respiratory support. However, acquiring CPAP is challenging due to its cost, not only for the machine but also for the accompanying staff required for daily home visits. Pediatric lung transplantation presents another difficult decision for the family, given the 50% success rate and the limited availability of centers capable of performing this procedure worldwide. Despite the emergence of new treatments for conditions due to mutations in SFTPC, treating these rare patients remains a challenge for pediatricians.

Keywords: *Childhood interstitial lung disease, mutations inSFTPC gene, surfactant metabolism disorders.*

I. INTRODUCTION

Surfactant metabolism dysfunction due to SFTPC gene mutations is a rare inherited interstitial lung disease with early onset, often presenting with persistent respiratory distress and interstitial lung disease in preterm or young infants. Pathogenic variants in SFTPC disrupt the synthesis and function of surfactant protein C, leading to alveolar type II cell injury and progressive lung disease. Diagnosis relies on clinical features, imaging findings, and molecular genetic testing. The aim of this report is to describe the clinical, radiological, and genetic characteristics of two preterm twin infants with interstitial lung disease caused by pathogenic SFTPC mutations.

II. CASE REPORT

Case 1: T.H.V, female, DOB: 28/10/2022, 16 months old.

Past medical history:

- The twin babies were born prematurely at 35 weeks with a birth weight of 2.1 kg.

- One of the twins experienced pneumonia at 3 months old, requiring ventilation support and subsequently becoming dependent on oxygen support.

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- A pathogenic missense variant c.218T>C (p.Ile73Thr) in *SFTPC* was identified by next generation sequencing, leading to surfactant metabolism dysfunction.

- The family history is reported as normal.

Physical examination:

- Chronic respiratory failure is present, along with finger clubbing.

- Lung auscultation reveals normal findings.

- There is no evidence of heart failure.

- Cushing's syndrome is confirmed.

- Oxygen saturation levels during unwell and stable periods range from a low of 68% to a high of 90%.

- At 16 months, the weight is reported as 7 kg. The feeding regimen includes Pediasure (120 ml per feeding, 5 times a day) and porridge (2 times a day).

- Non-invasive ventilation (NIV) support was required during an Adenoviral infection.

- Overnight sleep study shows stable oxygen saturation levels during sleep.

Table 1. Hematology profile

	WBC (10^9/l)	**Neutrophil%**	**Lymphocyte %**	**Eosin %**	**Hb** (g/l)	**PLT** (10^9/l)	**MCV** fL
17/02/2023	28.84	54.2	38.3	0.3	100	615	71.7
20/02/2023	10.64	54	38.2	0.9	89	371	68.6
8/05/2023	10.04	48.1	35.8	0.4	131	418	70.7
21/07/2023	13.77	48.7	45.0	1.2	121	475	75
08/08/2023	15.23	36.7	56.6	1.3	107	516	68.9
13/09/2023	7.37	69.8	26.0	0.1	107	447	62.4
16/11/2023	11.42	45.4	40.8	0.4	102	652	53.9
04/12/2023	15.88	59.8	28.1	0.8	95	900	58.4
18/12/2023	6.4	62.9	30.4	1.1	104	421	59.7

Table 2. Biochemistry profile in 2023

	Glucose (mmol/l)	**Ure (mmol/l) /creatinine** (µmol/l)	**GOT/GPT** (UI/l)	**Albumin/ Protein** (g/l)	**Na/K/Cl** (mmol/l)	**CRP** (mg/l)	**Procalcitonin** (ng/l)
17/2	3.87	4.9/30	95.6/63.9	33.8/58.1	125/5.0/91	6.33	-
18/2	3.91	-	-	-	146/3.7/117	-	14.66
20/2	-	2.6/18	60.9/178.6	26.2/49.5	140.5/3.99/110.5	57.12	-
8/5	-	3.6/19	53.6/17.9	40.3/64.4	133/5.2/102	1.94	-
13/9	-	3.11/33.1	45.7/18.2	-	135.9/5.01/103.5	-	-
20/11	-	3.1/34	45.4/119.7	36.0/54.7	140/3.7/100	-	-
18/12	-	3.7/13.9	83.0/62.0	42.8/68.6	137/4.33/102	27.53	-

18/2: Urinary osmotic pressure: 168 mOsmol/kg

21/2: IgA: 0.36; IgG: 4.52; IgM: 2.09 (g/l)

21/7: IgA: 1.56; IgG: 9.03; IgM: 2.49 (g/l)

8/8: RF: 13.49; C3: 1.06; C4: 0.11

9/8: anti-ANA: negative; dsDNA: 11.1

30/8: ACTH: 4.08 →16/11: 1.06pmol/l

16/11: Cortisol: 43.6 nmol/l

Coagulation: in a normal range

Biology profile: HBsAg, HCV, CMV, EBV, HIV negative.

Chest Xray

23/2/2023 19/12/2023

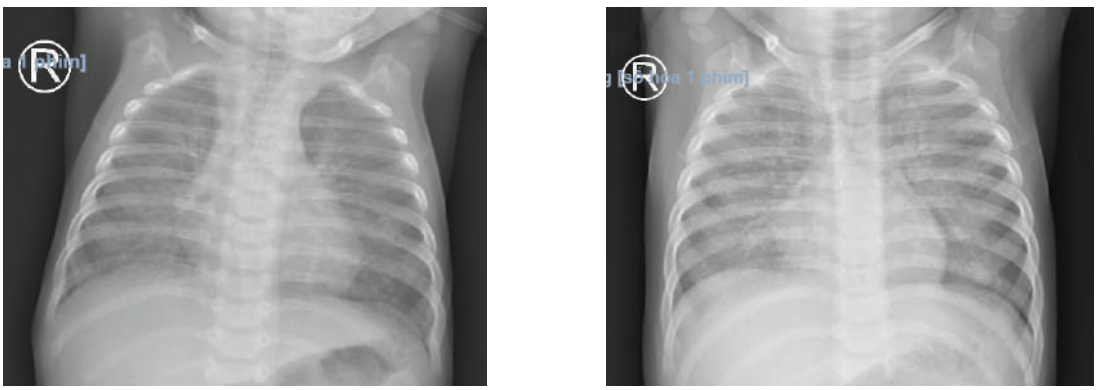


Figure 1. X-ray anterior-posterior view of the chest showing bilateral interstitial infiltrates and diffuse opacities.

Chest CT

30/3/2023

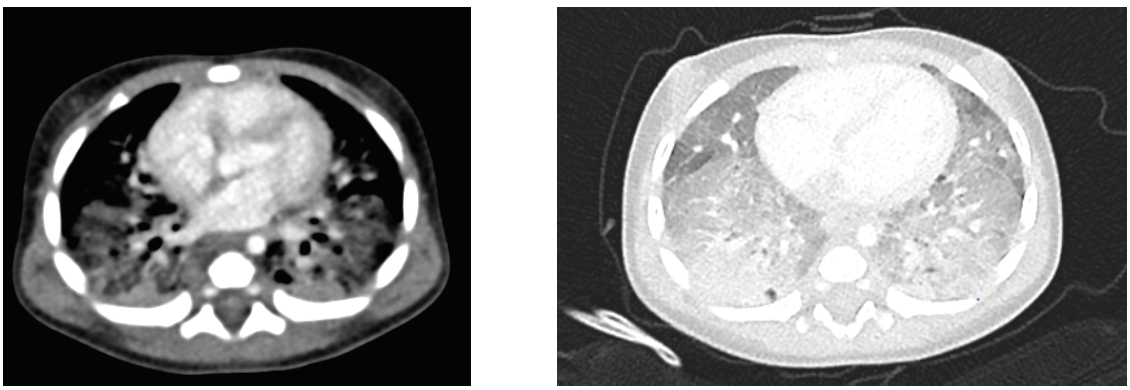


Figure 2. CT shows bilateral ground-glass and alveolar opacities.

Follow up:

Date	
17/2/2023	Acute respiratory failure, interstitial pneumonia: ventilation support in 20 days
08/05/2023	Bronchopneumonia
21/7/2023	Acute respiratory failure: ventilation support in 3 days
30/8/2023	Respiratory failure, interstitial pneumonia, Prednisolone + hydroxychloroquine
17/11/2023	Respiratory failure, interstitial pneumonia, Prednisolone + hydroxychloroquine

Case 2: Her twin sister, T.M.A, 16 months old, female, DOB: 28/10/2022

Medical history:

- The twin babies were born prematurely at 35 weeks with a birth weight of 2.1 kg.

- One of the twins experienced pneumonia at 3 months of age, requiring ventilation support, and subsequently became dependent on oxygen support.

- A pathogenic missense variant c.218T>C (p.Ile73Thr) in SFTPCwas identified by next generation sequencing, leading to surfactant metabolism dysfunction.

- The family history is reported as normal.

Physical examination:

- Chronic respiratory failure is present, along with finger clubbing.

- Oxygen saturation levels during unwell and stable periods range from a low of 75% to a high of 95%.

- Oxygen support at a rate of 1 liter per minute is provided and remains stable.

- Lung auscultation reveals normal findings.

- There is no evidence of heart failure.

- Cushing's syndrome is confirmed.

- At 16 months, the weight is reported as 6.5 kg. The feeding regimen includes Pediasure (120 ml per feeding, 5 times a day) and porridge (2 times a day).

Investigations in 2023

Table 3. Hematology

	WBC (10^9/l)	**Neutrophil%**	**Lympho%**	**Eosin%**	**Hb** (g/l)	**PLT** (10^9/l)	**MCV** fL
23/3/2023	8.19	69.1	27.2	0.1	102	773	61.5
08/05/2023	10.92	55.0	35.4	1.0	126	554	68
21/07/2023	10.69	47.9	42.8	0.4	128	432	71.3
30/08/2023	14.26	39.6	49.3	1.6	134	642	69.7

Table 4. Biochemistry

	Ure (mmol/l) **/Cre** (µmol/l)	**GOT/GPT** (UI/L)	**Albumin/protein** (g/l)	**Na/K/Cl** (mmol/l)	**CRP** (mg/l)	**Procalcitonin** (ng/l)	**proBNP** (pmol/l)
23/3	-	-	-	-	< 4.0	-	-
29/3		-	-	-	-	0.225	-
8/5	3.6/18	53.7/16.6	38.5/66.4	135/4.5/106	2.04	-	50.1
28/5	2.9/59.3	146.3/115.7	33.5/59.3	135/4.6/105	3.06	-	28.9
1/6	2.4/9.7	81.5/89.1	31.4/53.6	-	-	0.23	-
21/7	2.59/24.55	72.0/52.	-	138.3/4.51/103.2	0.74	-	26.4
30/8	2.6/18.3	63.0/67.5	-	135/4.9/106	< 4	-	26

24/3: 25OH-D: 62.36 (nmol/l); T3: 2.06 nmol/l; FT4pmol/l: 17.0; TSH: 3.65mUI/l

31/5: CMV IgM: positive 3.73; CMV IgG: positive 10.23; → 15/6: CMV: negative.

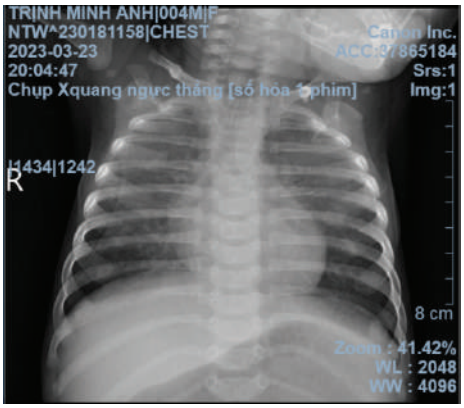
29/6: ACTH: 1.53 → 30/8: ACTH: 4.58 (pmol/l)

HBsAg, HCV, EBV, HIV negative.

Coagulation: in a normal range

Chest Xray

23/3/2023



30/8/2023

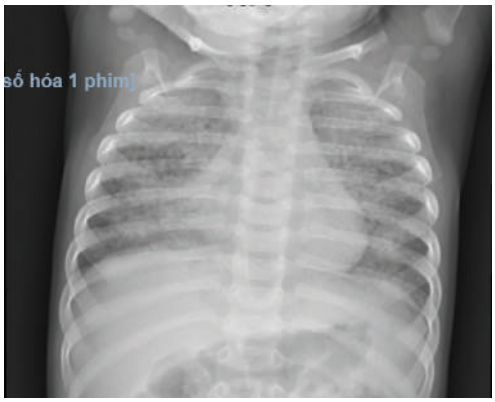
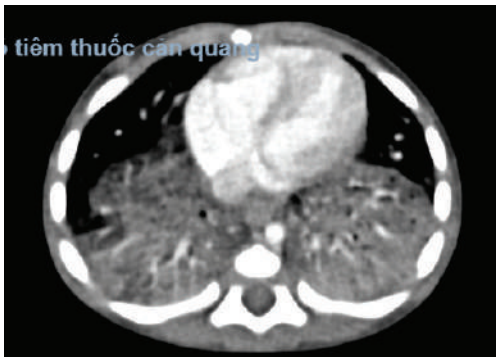


Figure 3. A. CXR image shows granular infiltration and slight opacification

B. CXR image shows diffuse streaky bilateral interstitial thickening and diffuse opacities.

Chest CT

30/5/2023



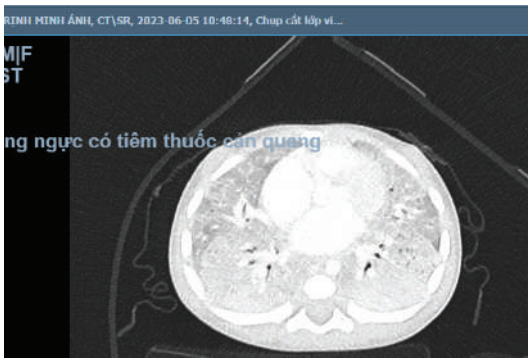


Figure 4. CT images show confluent opacification of the posterior aspects of the lungs, revealing pulmonary consolidation, diffuse ground-glass opacification, and discrete small cysts

Follow up:

Date	
23/3/2023	Bronchopneumonia, Acute respiratory failure: Breathe nasal oxygen for 15 days
08/05/2023	Interstitial pneumonia, respiratory failure
28/5/2023	Interstitial pneumonia, respiratory failure, Prednisolone + hydroxychloroquine
30/8/2023	Respiratory failure, interstitial pneumonia, Prednisolone + hydroxychloroquine

III. DISCUSSION

Childhood Interstitial Lung Disease (ChILD) is very rare in pediatrics, compared to adult ILD. Symptoms and presentation vary depending on their pathogenesis. We identified and classified childhood ILD according to the classification by N. Bernardinello et al [1]. The twin sisters exhibit symptoms consistent with Childhood Interstitial Lung Disease (ChILD), including respiratory symptoms, respiratory signs such as digital clubbing, failure to thrive, hypoxemia, and diffuse radiological changes.

Table 5. Distribution of child diagnoses and subgroup

Diagnosis/categories	Percentage of patients
NEHI	23%
Connective tissue diseases-related/immunomediated	16.5%
Systemic sclerosis	
Systemic lupus erythematosus	
Other	
Surfactant dysfunction	12%
Bronchiolitis obliterans	11%
Alveolar hemorrhage	9.2%
Alveolar growth disorders	4.8%
Others (including PAP, environmental/toxic drug-related, pulmonary interstitial glycogenosis)	13%
Unclassifiable ILD	11%

chILD: childhood interstitial lung disease ILD: interstitial lung disease NEHI: neuroendocrine cell hyperplasia of infancy PAP: pulmonary alveolar proteinosis

Following the presentation of symptoms, a comprehensive diagnostic workup was performed for the twin sisters. This included a full blood count, gene analysis, bronchoscopy to exclude pulmonary hemorrhage, as well as immunological and autoimmune testing.

Here we present twin cases afflicted with Childhood Interstitial Lung Disease (ChILD) attributed to a gene mutation affecting the surfactant mechanism. Upon observing respiratory distress shortly after birth, which could not be solely attributed to premature pneumonia, we opted to sequence genes associated with Interstitial Lung Disease (ILD). SFTPC is among the genes known to cause surfactant disorders in childhood ILD. Lung disease stemming from SP-C dysfunction is rare, and its prevalence is challenging to accurately determine. While precise information regarding the disease phenotype is not readily accessible, numerous pathogenic variants of the SFTPC gene are documented in genome AD, hinting at a prevalence of approximately 1 in 20,000 individuals [3]. Over 35 autosomal dominant (AD) mutations in the SFTPC gene have been identified.

Mutations in the SFTPC gene, which are associated with surfactant dysfunction, impact the processing of the SP-C protein. These mutations result in a decrease or absence of mature SP-C and an accumulation of abnormal forms of SP-C. The absence of mature SP-C leads to an abnormal composition of surfactant and a reduction in its function. Additionally, improperly processed SP-C proteins adopt incorrect three-dimensional shapes and accumulate within lung cells. This accumulation triggers a cellular response that leads to damage and ultimately cell death. Consequently, this damage disrupts the production and release of surfactant, exacerbating the underlying condition.

Unfortunately, it remains unclear which of the described outcomes directly contribute to the signs and symptoms associated with SP-C dysfunction. Our treatment approach involves administering corticosteroids, hydroxychloroquine, and azithromycin, guided by the Delphi consensus [4]. While these interventions effectively alleviate acute respiratory distress, patients continue to experience chronic respiratory distress, necessitating home oxygen support. We also recommend continuous positive airway pressure (CPAP) therapy at home; however, financial constraints prevent the acquisition of CPAP

devices and the hiring of healthcare professionals for daily monitoring. To address this, we advised the mother to bring the children to the hospital monthly for a bolus of methylprednisolone at a dosage of 10 mg/kg/day for 3 consecutive days. Regrettably, the family opted to keep their children at home to minimize the risk of infection at the hospital.

Emerging treatments for surfactant dysfunction, such as Ivacaftor, Genistein, and Granulocyte-macrophage colony-stimulating factor (GM-CSF), Cyclosporine A, show promise in addressing this condition [1]. However, assessing the clinical response in a cohort of rare patients requires considerable time and effort.

Table 6. Doses of medication to be used and anticipated time to assess if there has been a clinical response.

Medication	chILD ventilated or close to ventilation	chILD not ventilated or close to ventilation
Methylprednisolone	Dose: Intravenous 10 mg/kg or 500 mg/m^2 Response rate: 7 days Comment: 30 mg/kg used by some centres	Dose: Intravenous 10 mg/kg or 500 mg/m^2 Response rate: 28 days Comment: As alternative to oral prednisolone. Use before other therapies and judge response
Prednisolone	Dose: Oral 1 mg/kg used in between pulses of methylprednisolone Response rate: 7 days	Dose: Oral 2 mg/kg, as alternative to methylprednisolone pulses Response rate: 28 days Comment: Judge response
Hydroxychloroquine	Dose: 10 mg/kg Response rate: 21-28 days Comment: In children <6 years 6.5 mg/kg in some centres to reduce toxicity	Dose: 10 mg/kg Response rate: 3 months Comment: In children <6 years 6.5 mg/kg in some centres to reduce toxicity. No preference over azithromycin as second line. 54% would consider hydroxychloroquine as sole therapy in mild stable chILD
Azithromycin	Dose: 10 mg/kg 3 days per week Response rate: 3 months	Dose: 10 mg/kg 3 days per week Response rate: 3 months Comment: No preference over hydroxychloroquine as second line. 51% would consider azithromycin as sole therapy in mild stable chILD

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