



Early Diagnosis of a Case of Infantile Cystic Fibrosis and Review of Literature in Taiwan

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Few cystic fibrosis (CF) cases in Taiwan have been published. We report a case of 2.5-month-old male infant presented recurrent infection, failure to thrive, and nutritional deficiency dermatitis initially. Sweat chloride test confirmed the diagnosis at 4 months old. We highlight that CF should always be the differential diagnosis of patient with failure to thrive and recurrent pulmonary infections.

Key words: Cystic fibrosis, failure to thrive, infant, infection, steatorrhea

INTRODUCTION

Cystic fibrosis (CF) is a genetically inherited autosomal-recessive disease, resulting from mutations to the CF transmembrane conductance regulator (CFTR) protein, located on the long arm of chromosome 7. It is a multisystem disease typified by chronic respiratory tract infection, leading to bronchiectasis and end-stage lung disease. Only a few CF cases in Taiwan have been published.¹⁻³ We report the first CF case diagnosed in infancy with complete laboratory and molecular tests in Taiwan IRB No. 1-107-05-013. Consent form is not obligatory for patient whose history has been more than 3 years.

CASE HISTORY

A full-term male infant was born after a normal pregnancy and vaginal delivery (gestational age: 39 weeks, G2P2; birth weight: 2965 g). At 1 month of age, the infant had *Escherichia coli* and *Enterococcus faecalis* urinary tract infection. Then, at 2.5 months, he was hospitalized because of a cough for 1 week duration. Physical examination showed a failure to thrive; his body height (55 cm), body weight (3.96 kg), and head circumference (37 cm) were less than the third percentile on the normal growth curve.

He had pitting edema in his extremities, skin desquamation with erythematous change [Figure 1], and

copious greenish, loose stool. Pneumonia, a urinary tract infection, and a yeast infection were suspected, and he received empiric antibiotics and antifungal agents with ampicillin, gentamicin, and fluconazole. Urinary cultures grew *E. coli* and *E. faecalis*; sputum culture grew *Candida albicans*. Urine cytomegalovirus polymerase chain reaction also showed positive. He also had normocytic anemia (Hb = 7.2 g/dL, mean corpuscular volume = 82.8 fL), hypoalbuminemia (albumin = 2.0 g/dL), and hyponatremia (Na = 130 mmol/L). He received a blood transfusion and albumin supplementation.

A dermatologist was consulted, and then, pityriasis alba, reactive dermatitis, and zinc deficiency were suspected. Due to his clinical features including recurrent infection and failure to thrive, we suspected that he might have immunodeficiency or CF. A series of immunologic study was applied which revealed normal finding (C3 = 45.7 mg/dL, C4 = 17.8 mg/dL, IgG = 381 mg/dL, IgM = 34 mg/dL, IgA = 20 mg/dL). He was given pancreatic enzymes, vitamin supplements, and a zinc supplement. After treatment, the skin rash and stool improved significantly [Figure 1].

As sweat chloride test showed high chloride concentrations (110 mmol/L and 160 mmol/L at 4 and 4.5 months of age, respectively). A DNA analysis was performed and a homozygous nonsense

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How to cite this article: Lin HC, Huang SW, Lu YC, Wang CC. Early diagnosis of a Case of infantile cystic fibrosis and review of literature in Taiwan. J Med Sci 2019;39:90-3.

Received: August 08, 2018; Revised: August 08, 2018;

Accepted: August 20, 2018

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mutation c.923C>A (p.S308X) and a homozygous variable-site mutation c.1408G>A (p.V470M) (NCBI: SNP rs213950) in the *CFTR* gene were identified [Figure 2], confirming CF.

DISCUSSION

CF is a major, severe, chronic lung disease in White populations but is rare in Asian populations, with a reported incidence of <1 in 50,000. Mutations in the *CFTR* gene leads to an inability to secrete salt and water with excessive reabsorption of salt and water, leading to secretions that obstruct the airways, pancreatic ducts, biliary ducts, and vas deferens. CF is characterized by the classic triad of elevated sweat chloride levels, chronic sinopulmonary disease, and pancreatic insufficiency.



Figure 1: Coalescing erythematous plaques with overlying desquamation, manifested in the cheeks, proximal extremities, buttocks, and genitourinary region, improved after protease and zinc supplementation

In infants, the presentation of CF includes meconium ileus and failure to thrive. About 15% of infants with CF are born with meconium ileus, and of these, 85%–90% develop pancreatic insufficiency in the 1st year of life. Symptoms include steatorrhea and failure to gain weight even with large food intake. Severe, untreated pancreatic insufficiency can present with protein-energy malnutrition, anasarca, hypoproteinemia, electrolyte loss, anemia, and failure to thrive. Nutritional deficiency dermatitis may be present as the initial manifestation of CF.⁴ It can present at 2 weeks to 6 months of age due to essential fatty acids, Vitamin E, zinc, and possible taurine and copper deficits.⁵

Our infant patient fulfilled the diagnostic criteria for CF. He had elevated sweat chloride combined with symptoms including failure to thrive, protein-energy malnutrition, nutrition deficit disorder, and steatorrhea.

The most prevalent mutation of *CFTR* is deletion of a single phenylalanine residue at amino acid 508. We identified a homozygous nonsense mutation c.923C>A (p.S308X) and a homozygous variable-site mutation c.1408G>A (p.V470M) (NCBI: SNP rs213950) in our infant patient. The c.1408G>A (p.V470M) is a single nucleotide variant on 7q31.2 which does not cause CF when combined with another CF-causing variant based on CFTR2 database.⁶ Thus, we believed that p.S308X is a novel mutation that cause CF.

Similar clinical presentations have also been noted in these patients reported in Taiwan [Table 1] who had the onset of symptoms in infancy and died at an early age. Only two Taiwanese cases of CF diagnosed in infancy have been reported in the medical literature.

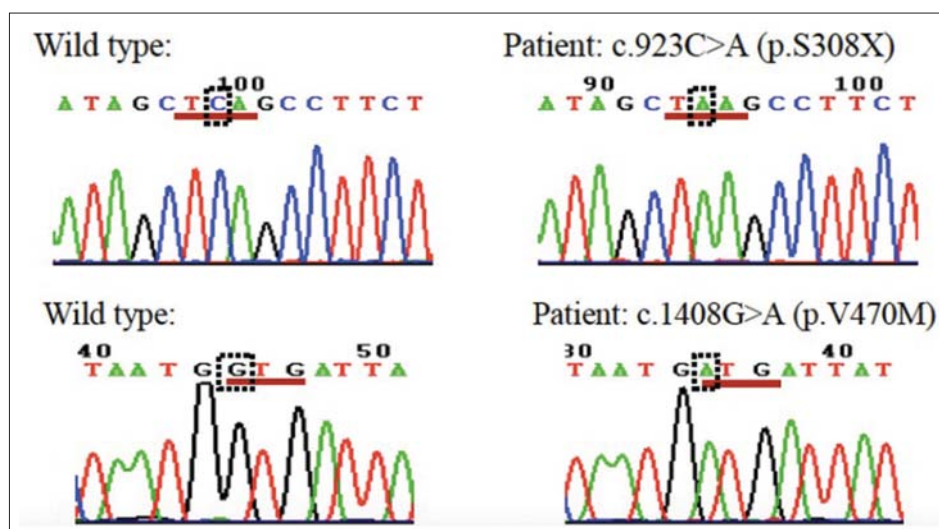


Figure 2: We screened for mutations in all the coding sequence and exon-intron boundaries of the cystic fibrosis transmembrane conductance regulator by polymerase chain reaction and direct sequencing

Table 1: Cystic fibrosis transmembrane conductance regulator mutations and clinical manifestations in Taiwanese patients

Patient (reference)	Gender	Age at diagnosis	Family history	Symptom onset	Clinical manifestation	Sweat chloride test (mmol/L)	Genetic analysis	Current clinical conditions
1. Our patient	Male	4 months	None	2.5 months old	Failure to thrive Recurrent infection	110,160	c.923C>A/c.923C> A (novel) c.1408G>A	Bronchiectasis, no limitation of physical activity
2. Liu <i>et al.</i> , 2014 ¹	Female	20 years	Two sister died due to pneumonia and bronchiectasis at 4 months old and 16 years old	before 13 years old	Recurrent pneumonia		3849+10kb C>T/3849+10kb C>T	Bronchiectasis
3. Liu <i>et al.</i> , 2014 ¹	Male	16 years	Younger brother have similar presentation	2 months old	Recurrent pneumonia		1898+5G > T/p.I1023R (novel)	Bed-ridden but improved after receiving tobramycin
4. Liu <i>et al.</i> , 2014 ¹	Male	16 years	Younger brother of Case 2	5 years old	Recurrent pneumonia		1898+5G > T/p.I1023R	Bronchiectasis
5. Liu <i>et al.</i> , 2014 ¹	Male	8 years		2 months old	Failure to thrive Recurrent pneumonia		R553X/R553X	Bronchiectasis complicated with cor pulmonale
6. Chen <i>et al.</i> , 2005 ²	Male	3 years		2 months old	Failure to thrive, Recurrent pneumonia		R553X/R553X	Chronic hypoxemia and pancreatic insufficiency
7. Wong <i>et al.</i> , 2003 ⁸	Male	2 years	Autopsy of sister revealed CF	1 year old	Failure to thrive, Recurrent UTI, pneumonia	89		
8. Alper <i>et al.</i> , 2003 ⁹	Male	1 years 6 months	Older sister had CF found at autopsy; Vietnamese mother				E7X and 989-992insA	Died at 2 years
9. Wu <i>et al.</i> , 2000 ¹⁰	Female	14 years	Sibling of patient		Failure to thrive, Recurrent pneumonia	327	1898 + 5G>T/2215insG	Bronchiectasis
10. Wang <i>et al.</i> , 1993 ⁷	Female	9 months	Older brother died at 8 months with similar symptoms	Since birth	Failure to thrive, Recurrent pneumonia			Died at 16 months, autopsy proved
11. Wang <i>et al.</i> , 1993 ⁷	Female	6 months	Older brother died at 6 months with similar symptoms	Since birth	Failure to thrive, recurrent pneumonia		1898+5G fi T	Milder respiratory symptoms and pancreatic insufficiency

UTI: Urinary tract infection, CF: Cystic fibrosis

Clinical presentations of these two infants showed recurrent pneumonia and poor weight gain. One infant died at 16 months of age; autopsy revealed mucus-plugged, dilated exocrine ducts in the pancreas.⁷ CF patients reported in Taiwan have diverse novel CFTR mutations [Table 1]. This finding means the absolute number of carriers is in the millions. The incidence of CF in Taiwan may in fact be higher than expected. The delay in diagnosis of CF could have been due to the

belief that in Taiwan, it is not necessary to include CF in the differential diagnoses of failure to thrive.

CONCLUSION

A high index of clinical suspicion is mandatory for early detection and prompt treatment of infantile CF. In infants with failure to thrive and recurrent pulmonary infections,

we should always include CF in the differential diagnosis. Earlier diagnosis and aggressive treatment are the only ways to improve the prognosis of Asian patients with CF.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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