Journal of Microbiology, Immunology and Infection (2014) 47, 358–361

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CASE REPORT

Cystic fibrosis: Experience in one institution

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Received 14 September 2011; received in revised form 17 December 2011; accepted 11 May 2012
Available online 16 September 2012

KEYWORDS
Cystic fibrosis;
Cystic fibrosis transmembrane conductance regulator gene (CFTR gene);
Taiwan

Cystic fibrosis (CF) is one of the most common autosomal recessive inherited disorders among Caucasians. Comparatively, it is considered to be a rare disease among Asians. To date, only a few cases of Taiwanese CF have been published. We report four CF cases from three families. Case 1 was the first report of CF associated with a homozygosity for the CF transmembrane conductance regulator gene (CFTR gene) mutation 3849+10kb C->T in a Taiwanese patient. Cases 2 and 3 had heterozygous c. 1898+5 G->T and heterozygous p. I1023R (novel mutation) for the CFTR gene mutation. Case 4 was homozygous for the CFTR gene mutation R553X being reported in 2005 and complicated with cor pulmonale. These four patients had received 300 mg bid aerosolized tobramycin treatment every other month.

Introduction

Cystic fibrosis (CF), an epithelial cell transport disorder caused by mutations of the CF transmembrane conductance regulator (CFTR) gene, is an autosomal recessive inherited disorder of exocrine gland function, involving multiple organ systems. CF is uncommon in Africa and Asia, with a reported frequency of 1 in 350,000 in Japan.[1] Previous studies reported that CF is quite rare among Taiwanese, and until now, only 10 Taiwanese patients with CF (from eight different families) have been reported.[2,3] However, we believe that the rate of CF is underestimated in Taiwan, and that this may be due to our clinicians seldom believing it to be one of the differential diagnoses.

Case reports

Case 1

The patient was a 20-year-old female who had frequent diarrhea and sinusitis with purulent nasal discharge and

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1684-1182/$36
http://dx.doi.org/10.1016/j.jmii.2012.06.005

nasal polyps before she was 13 years of age. Repeated hospitalizations because of pneumonia with *Pseudomonas aeruginosa* (*P. aeruginosa*) infection and bronchiectasis with acute exacerbation were noted. In addition, secondary amenorrhea 4 years ago and acute pancreatitis 2 years before were also noted.

Tracing back her family history, the patient had one healthy younger brother, but her older sister had died at 4 months old with pneumonia, and her younger sister, who had panbronchiolitis and bronchiectasis with recurrent *P. aeruginosa* pneumonia, also expired at 16 years old due to bronchiectasis and pneumothorax.

Her chest roentgenogram demonstrated hyperinflation, interstitial pneumonitis with emphysema and tramline appearance. High-resolution computed tomography showed peribronchial thickening and bronchiectasis throughout both lungs.

According to her clinical features, laboratory findings and family history, CF was highly suspected. DNA analysis was performed by direct sequencing of genomic DNA to screen the entire CFTR gene and homozygosity for the CFTR gene mutation 3849+10kb C->T was identified.

The patient's mother and younger brother were heterozygous for the CFTR gene mutation 3849+10kb C->T (Fig. 1) and there were no clinical manifestations. Their father did not receive DNA analysis. Nevertheless, because the patient was homozygous for the CFTR gene mutation 3849+10kb C->T, we consider that her father must be the carrier of the heterozygous 3849+10kb C->T gene mutation too. Furthermore, although her younger sister had a negative sweat chloride test, we still highly suspect that she had CF and was homozygous for the CFTR gene mutation 3849+10kb C->T, because the gene mutation of 3849+10kb C>T is found in patients with a normal sweat chloride test.

Case 2

The patient, a 17-year-old boy with clubbing fingers, was the first child of unrelated, healthy, native Taiwanese parents. He had nasal obstruction and recurrent sinusitis since early childhood and had received functional endoscopic sinus surgery (FESS) at 14 years of age. A persistent night cough was noted since he was 2 months old, which became productive and progressively worse since he was 8 years old. He was repeatedly hospitalized due to frequent bronchiolitis and pneumonia since early childhood. *P. aeruginosa* pneumonia and methicillin resistant *Staphylococcus aureus* (MRSA) pneumonia were proven by sputum cultures numerous times. There were six pneumothorax attacks since the age of 12 and pleurodesis at 15 years of age. His chest roentgenogram showed diffused bronchiectasis. Pulmonary function tests revealed: FEV1 = 1.12 L (37%), FVC = 2.05 L (56%), FEV1/FVC = 54%, FEF $_{25-75\%}$ = 10% and TLC = 3.3 L (73%). The flow-volume curve scooped out with a reduced flow-volume slope and low flows.

CF was suspected due to recurrent *P. aeruginosa* pneumonia and pneumothorax and was confirmed by gene analysis with heterozygous c. 1898+5 G->T and heterozygous p. I1023R mutation (novel mutation) at the age of 16 years. His mother had a heterozygous mutation in p. I1023R and his father had a heterozygous mutation in c. 1898+5 G->T (Fig. 2). The patient became bed-ridden and oxygen dependent at 16 years of age. After receiving tobramycin 300 mg bid every other month, he could walk by himself and oxygen was needed occasionally when sleeping at night.

Case 3

The patient, a 16-year-old boy, was the younger brother of Case 2. He also had recurrent sinusitis and nasal obstruction with progressing severity since 5 years of age and had received FESS at the age of 14. A dry cough had been noted since he was 12 years old, which became productive and progressively worse at 13 years of age. Recurrent *P. aeruginosa* pneumonia was also noted. His chest roentgenogram demonstrated diffused bronchiectasis. Pulmonary function tests revealed FEV1 = 2.35 L (61%), FVC = 2.87 L (64%), FEV1/FVC = 82%, FEF $_{25-75\%}$ = 55% and TLC = 4.12 L (80%). The slope of flow-volume curve was increased.

CF was suspected and also confirmed by DNA analysis, with heterozygous c. 1898+5 G->T and heterozygous p. I1023R mutations (Fig. 2). In addition, due to intermittent abdominal pain and heartburn sensation, a further survey of the abdomen revealed gastroesophageal reflux, a duodenal polyp and a hepatic hyperechoic lesion (16.7 × 7.0 × 7.4 mm).

Case 4

An 8-year-old boy had chronic diarrhea and a failure to thrive from the age of 2 months. He was also repeatedly hospitalized because of pneumonia with *P. aeruginosa* and

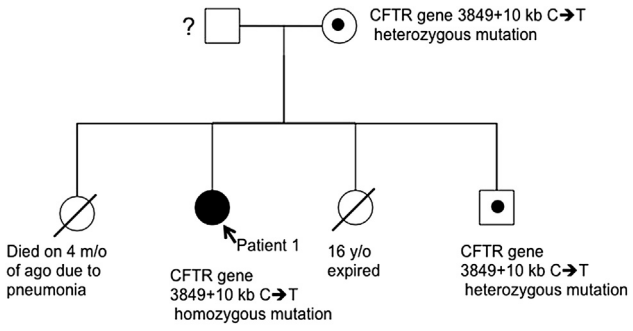

Figure 1. The pedigree of patient 1.

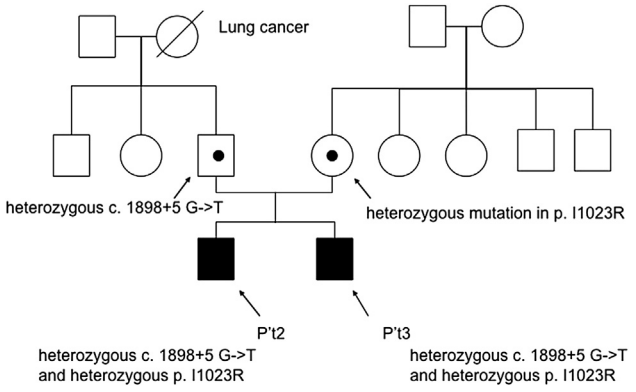

Figure 2. The pedigree of patients 2 & 3.

Staphylococcus aureus (*S. aureus*) infectionssince early childhood and had diffuse progressing bronchiectasis. In addition, he had pancreatic insufficiency with fat malabsorption. His weight and height were both below the third percentile. His chest roentgenogram demonstrated diffuse bronchiectasis. High-resolution computed tomography demonstrated peribronchial thickening, multiple areas of bronchiectasis, and sputum plugs in both lung cavities.

CF was suspected and confirmed by DNA analysis with homozygosity for the CFTR gene mutation R553X. Both of his parents were heterozygous for the CFTR gene mutation R553X (Fig. 3). His cardiac sonography showed severely dilated right atrium (RA), right ventricle (RV), severe tricuspid regurgitation (TR), pulmonary hypertension (pressure gradient (PG) = 63.8 mmHg) and minimal pericardia effusion. The final diagnosis was CF with diffuse bronchiectasis complicated with cor pulmonale.

Discussion

CF involves multiple organ systems, including the respiratory tract, the gastrointestinal tract, the genitourinary tract and the sweat glands. It is the major cause of severe chronic lung disease in Caucasians. In Asian populations, the disease is rarely diagnosed definitively.

The CFTR gene is expressed in epithelial cells of the respiratory tract, the gastrointestinal tract, the genitourinary tract and the sweat glands. Defects in the 7q CFTR gene, which encodes for a protein of regulatory function of the chloride channel, produced a decrease in the secretion of chloride and an increase in the reabsorption of sodium and H_2Oacross epithelial cells. A deficiency of water in the mucous leads to a failure to clear mucous secretions.[4] These secretions are retained in the airways, the pancreatic ducts, the biliary ducts and the vas deferens which obstruct the canals, leading to dysfunction and increased salt content in sweat and other serous secretions.

More than 1500 CFTR polymorphisms of five different classes have been described. The gene mutation in Case 1 was 3849+10kb C→T, which has an incidence of about 0.7% worldwide.[5] Cases 2 and 3 had heterozygous c. 1898+5 G->T and heterozygous p. I1023R mutations. A point mutation (1898 + 5G->T), located five base pairs downstream from the donor splice site in intron 12 of the CFTR gene, has been identified in CF patients of East Asian lineage, especially those of Chinese origin.

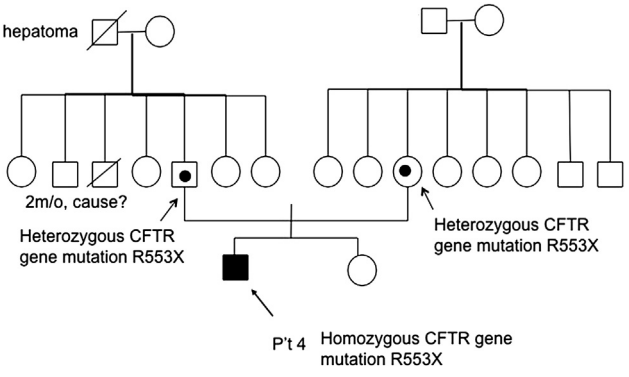

Figure 3. The pedigree of patient 4.

In addition to Cases 2 and 3 in this report, the nucleotide mutation of c. 1898+5 G->T was reported previously in four Taiwanese patients.[2] The homozygous R553X mutation in Case 4 had defective regulation and the CFTR was not activated by ATP or cyclic AMP; this is accounted for in 0.9% of CF patients. Most of the R553X mutations are heterozygous and only two cases of homozygosity for R553X have been reported to date.[2,5]

The clinical manifestations of CF vary. Chronic cough with purulent expectorated sputum and frequent pneumonia and bronchiolitis are the most common symptoms, accompanied by a high prevalence of airways colonization with *S. aureus* and *P. aeruginosa* (rare in other individuals). All of our patients had recurrent pulmonary infections. Pneumothorax occurs more frequently in older patients, about 5–8% of CF patients, as compared to children and teenagers. Pancreatic insufficiency induced by maldigestion and malabsorption of fats and proteins (a hallmark of the disease, 90% of patients by 1 year of age) is primarily responsible for the failure to thrive. Gastroesophageal reflux is more common in patients with CF than in normal control patients. Case 3 also had this problem. Biliary cirrhosis becomes symptomatic in only 2–3% of patients. Puberty is usually delayed due to nutritional factors. Adolescent females may experience secondary amenorrhea, especially with exacerbations of pulmonary disease, such as in Case 1. Sweat is abnormally high in sodium and chloride, both at rest and during exercise. Some CFTR mutations, such as 3849+10kb C→T and Arg117His–7T mutations have preserved sweat duct function.[5] Case 1 had a homozygous 3849+10kb C->T gene mutation and normal sweat chloride concentrations. CF complicated with cor pulmonale was first reported at 1951. Autopsies have shown cardiac involvement in 70% of children dying from CF; only 15% of these patients showed clinical right heart failure. In CF, bronchial wall and parenchymal damage reduce intrapulmonary gas exchange. Alveolar hypoxia, chronic inflammatory process and hypercapnia lead to pulmonary vasoconstriction, pulmonary hypertension and alteration of right ventricular structure or function. Right ventricular failure occurs in 46% of CF patients at least 2 weeks before death.[6]

A diagnosis of CF is based on laboratory evidence for CFTR dysfunction, including two elevated sweat chloride concentrations obtained on separate days ($Cl > 60$ mEq/L) or the identification of two CF mutations or an abnormal nasal potential difference measurement, in conjunction with one or more of the following: presence of typical clinical features (respiratory, gastrointestinal, or genitourinary), a history of CF in a sibling, or a positive newborn screening test.[7]

Current CF treatments, which target respiratory infections, inflammation, mucociliary clearance, and nutritional status, are associated with improved pulmonary function and reduced exacerbations. The goal of therapy is to maintain patients in a stable condition for prolonged periods.

Aerosolized antibiotics, such as inhaled tobramycin, can suppress chronic *P. aeruginosa* infections in patients with moderate to severe disease, to improve lung function, reduce exacerbations and decrease the risk of hospitalization.[8] Macrolide antibiotics are effective in the treatment

of diffuse panbronchiolitis and several randomized, controlled clinical trials have had proven clinical benefits in CF.[9] Bronchodilators, such as β-adrenergic agonists, can relax smooth muscles, dilate bronchial passages, provide symptomatic relief and facilitate clearance of the airway.

Two major goals of treatment of CF with cor pulmonale are correction of hypoxemia and a decrease of RV after load. Bronchodilators, cardiac glycosides (digoxin), diuretics and vasodilators are effective in treating systemic venous congestion of cor pulmonale in CF. Patients with hypoxemia and cor pulmonale may benefit from long-term use of oxygen in terms of improved survival and intellectual function.[10]

Diet adjustments with regards to low fat, high protein, high calorie diet and pancreatic enzyme replacement and supplementary vitamins, are required to manage poor exocrine pancreatic function.

CF is a life-limiting disorder, with a median cumulative survival of 30 years. Lung disease accounts for nearly 85% of cases of mortality. An irreversible loss of pulmonary function from low-grade infection can occur gradually and without acute symptoms; early and aggressive treatment can improve the outcome. Patients whose respiratory tract cultures yield *P. aeruginosa* have a poorer outcome than those without these organisms.

We believe CF in Taiwan has been underestimated due to the lack of clinical suspicion. In patients with bronchiectasis and recurrent pulmonary infection, especially those with family history of early death, CF should be one of the differential diagnoses; aggressive intervention is indicated in such patients. In addition, regular evaluation and adjustments are indicated for subsequent complications.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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