Case Report of a Chinese Cystic Fibrosis Boy with the c.1521_1523delCTT/c.3874-4522A>G Genotypes

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Abstract

This report entails a case of an 11-year-old Chinese boy with cystic fibrosis (CF), who bears the c.1521_1523delCTT/c.3874-4522A>G genotype, which is extremely rare in Chinese population. Notably, the deep intron mutation c.3874-4522A>G was the first time identified among Chinese patients, which was reported mainly associated with mild phenotype. It is generally considered that a mild allele sustains *CFTR* function in a dominant fashion, even if paired with a severe allele. However, in the present report, the c.3874-4522A>G mutation was found related to severe pulmonary diseases, including early symptom onset, progressive bronchiectasis, recurrent airway *P. aeruginosa* combined with MRSA, rapid decline of lung function, and poor weight gain, which suggesting severe phenotype. Despite intensive chest care and optimized therapy, the child ultimately died of cardiopulmonary failure 3 months after discharge.

INTRODUCTION

Cystic fibrosis (CF) is a serious and life-shortening autosomal recessive disorder, affecting approximately 100,000 persons worldwide, and characterized by defective chloride transport channel in epithelial cells of exocrine tissues[1]. The progression of the disease may result in multi-system dysfunction, including sinopulmonary disease, meconium ileus, pancreatic insufficiency and sweat electrolyte abnormalities. To date, approximately 2000 mutations in the *CFTR* gene have been reported worldwide[2]. The epidemiology of CF is well studied in Caucasians from developed countries, however, the data on the incidence of CF in China mainly come from studies with small sample size or case reports over the past 4 decades. Up to now, only approximately 110 CF patients of Chinese origin were reported in literature[3]. In this report, we present a pediatric case with severe CF phenotype and c.1521_1523delCTT/c.3874-4522A>G genotype, which is extremely rare in Chinese population.

CASE REPORT

An 11-year-old Chinese boy presented with chronic coughing, expectoration, recurrent wheezing, and failure to thrive since his 2 months of age (Figure 1). He was frequently hospitalized due to recurrent pneumonia and repeated respiratory distress approximately 6-10 times per year. In between all the admissions, the patient still developed cough, wheeze, and occasional dyspnea. The first time he presented to Henan children's hospital was at his 7 years of age. Chest CT scan and bronchoscope both showed bronchiectasis with mucus plugging. Sputum/BALF culture was consistently positive with *P. aeruginosa* . Lung function rapid declined (FEV1 29.0%, FVC 33.0%). Due to a strong suspicion of CF, the first genetic test was performed. Unfortunately, only c.1521_1523delCTT variant on maternal allele was detected, without any variant observed on paternal allele. At 9 years of life, this patient got exercise intolerance and was unable

to wean off oxygen until now. Another airway organism MRSA was isolated, which was only sensitive to vancomycin.

At this time of admission, the boy presented in worse general condition. Physical examination revealed a poor nutritional status (peripheral oedema, weight < 3rd centile), hypoxemia with desaturation down to 80% on room air, tachypnoea with nasal flaring (respiratory rate of 36/min), bilateral generalized rhonchi and rales, hepatosplenomegaly, and finger clubbing. Repeated CT scan showed the deterioration of the lung structure and progressive bronchiectasis with extensive mucus plugging (Figure 2). Expanded genetic testing for CF revealed the c.3874-4522A>G variant deeply located in intron 23 of the paternal allele and the diagnosis of CF was eventually confirmed.

The boy was put on CPAP 7 days for worsening bronchospasm with CO_2 retention (73 mmHg), and weaned down to NPO_2 2L/min. He completed 14 days of IV antibiotic regimen (ceftazidime combined with vancomycin), and treated with inhaled hypertonic saline, inhaled tobramycin, and bronchoalveolar lavage (3 times) meanwhile. He got clinical improved and discharge on home oxygen therapy after 14 days. Bilateral lung transplantation was recommended. However, limited clinical experience and shortage of lung donors in China made transplantation difficult. 3 months after discharge, he died of cardiopulmonary failure.

DISCUSSION

The diagnosis of CF remains very difficult in China, due to inadequate awareness of the disease by Chinese physicians for decades, the inaccessibility of sweat chloride testing facility, as well as atypical clinical manifestations and different genetic spectrum compared to Caucasians[4]. It is well identified that the genotypic spectrum of CF varies widely among different populations based on their geographic and ethnic origins. The most common mutation in the Caucasians is c.1521_1523delCTT(p.F508del), with approximately 70% of patients being heterozygous for this mutation[5]. However, it is quite rarely seen in Asia, especially East Asia. The c.1521_1523delCTT (p.F508del) was only observed in 2 patients of Chinese origin currently (1 child in homozygosity and 1 adult in compound heterozygosity)[6, 7]. No cases have ever been reported in other East Asian countries so far. The parents of the child are both from Kaifeng City, Henan Province, which located in the central region of China. Historically, the Henan Province was ruled by the Mongol armies for 130 years. The Mongol armies were predominantly Mongolian, but they also included a small number of Caucasian. Based on this, we speculate that the origin of the c.1521_1523delCTT (p.F508del) variant in China most likely came from the Mongol armies, which may be due to the intermarriage between Chinese and Caucasians during the colonial period.

The first time the boy presented to us was at his 7 years of age. However, due to the limited sequencing methods at that time, we only detected a c.1521_1523delCTT variant on one allele. With the pathogenic role of deep intron mutations in CF disease are gradually recognized, 4 years later, we found the c.3874-4522A>G variant on the other allele and eventually supplemented the genetic data. The c.3874-4522A>G is a deep intron mutation that has never been reported in Chinese population. Bergougnoux et al [8]reported 10 cases with c.3874-4522A>G and found that c.3874-4522A>G is associated with divergent phenotypes, from milder phenotype including few symptoms, delayed symptom onset and better nutritional state (most of the cases) to typical CF with pancreatic insufficiency (only 1 case). In this report, the c.3874-4522A>G was found in a Chinese boy with severe pulmonary diseases from 2 months early infancy, including progressive bronchiectasis, significant lung function defect, and poor weight gain which suggesting severe phenotype. The phenotypic variability might be contributed to the modifier genes, encoding proteins involved in the defense against pathogens or in splicing regulation, and possibly an age-related exhaustion of the splicing machinery[8].

The estimated median survival age of CF patients, which is close to 50 years today[9], is expected to continue to improve in the future, with the recent advent of CFTR modulator therapies[10]. The major clinical characterization of Chinese individuals with CF was the presence of high frequency of respiratory disease[4]. Meanwhile, many studies demonstrate that progression to end-stage lung disease and death is more rapid in those with chronic *P. aeruginosa* infection than in those without[11]. Therefore, early eradication of*P. aerug-*

inosa treatment can improve the outcome significantly. We believe CF in China has been underestimated due to the lack of clinical suspicion and the inaccessibility of sweat chloride testing facility, which is the gold standard in diagnosing CF. In patients with unexplained bronchiectasis, meconium ileus, and steatorrhea, CF screening including genetic test need to be performed by Chinese pediatricians.

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ETHICS STATEMENT

Written consent was obtained from the patient's parents for publishing this case report.

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Figure 1. Timeline of the course of disease for an 11-year-old Chinese boy with CF

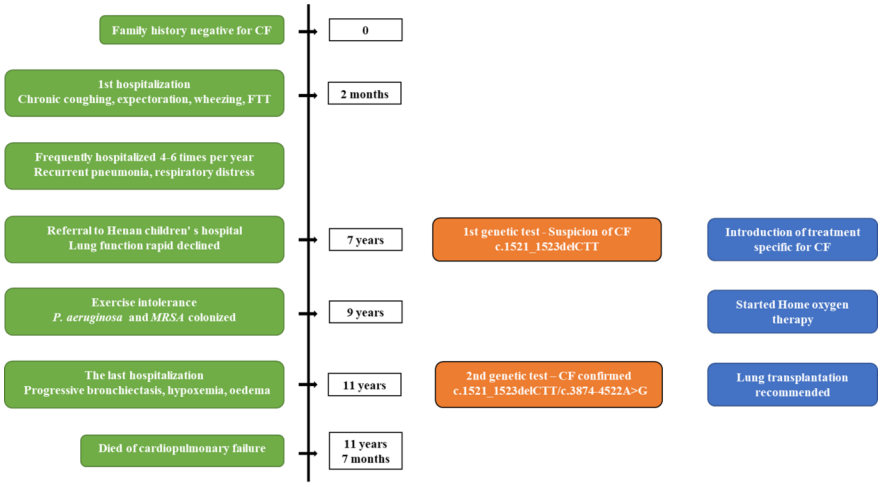
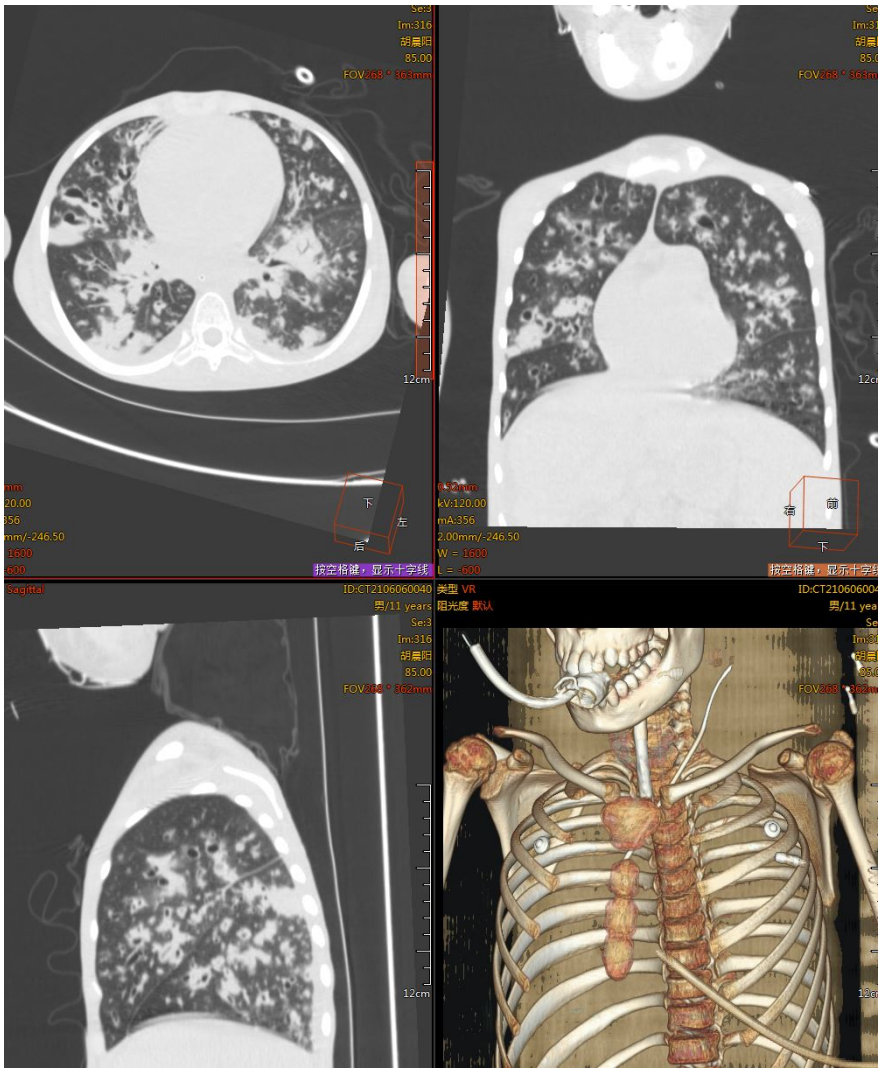


Figure 2. Chest CT images of a Chinese boy with CF at the first time presented to Henan children's hospital (A) and the last hospitalization before his death (B), showing the deterioration of the lung structure and progressive bronchiectasis with extensive mucus plugging.



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