CASE REPORT
[3120+1kbdel8.6kb]+[p.N1303K] GENOTYPE IN AN EMIRATI CYSTIC FIBROSIS PATIENT: INDICATION OF A FOUNDER MUTATION IN PALESTINIAN ARABS

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Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder in Caucasian population. The disease was initially considered to be rare in Middle Eastern countries. 95% of CF in Emirati families is due to two mutations only – p.S549R(T>G) and p.F508del. We report here the case of a patient referred to CF and Respiratory Clinic at Tawam Hospital for *cystic fibrosis transmembrane regulator (CFTR)* gene screening to ascertain the diagnosis of CF, who was found to carry a unique genotype, signifying the importance of retrieving ancestral histories of patients with monogenic disorders

Keywords: Cystic Fibrosis, autosomal recessive disorder, Genotype

INTRODUCTION

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder in Caucasian population.[1] It is a multisystem disorder characterized by a constellation of symptoms mainly including chronic bacterial infection of airways, pancreatic insufficiency, infertility in males and increased concentration of chloride in sweat.[1] It is caused by defect in a 190 kb gene on chromosome 7 encoding a 1480 amino acid polypeptide, named cystic fibrosis transmembrane regulator (CFTR).[1,2] To date 1523 *CFTR* gene mutations have been identified, responsible for CF or related diseases.[3]

Cystic fibrosis occurs in an estimated 1 in 2500 live births in Caucasians.[1] However its incidence is quite variable, and ranges from 1/500 in Ohio Amish to 1/90000 in Hawaiian Orientals.[1] The disease was initially considered to be rare in Middle Eastern countries.[4] However better awareness and improved diagnostic tools have suggested a higher incidence.[5] Since the startup of the first Cystic Fibrosis and Respiratory Clinic at Tawam hospital, Al Ain, U.A.E. in 1995, there has been an increased awareness on cystic fibrosis among general practitioners and pediatricians in the region.[6] In a study aimed at identifying the mutations responsible for the disease in the Emirati population, it was found that the pattern of CF-causing mutations is different in this population as compared to the other Arab populations in the region.[5-6] Indeed, 95% of CF in Emirati families is due to two mutations only – p.S549R(T>G) and p.F508del.[5] We report here the case of a patient referred to CF and Respiratory Clinic at Tawam Hospital for *CFTR* gene screening to ascertain the diagnosis of CF, who was found to carry a particular genotype.

CASE REPORT

The proband is a boy who was referred at 2 months of age. He was born to a non-consanguineous healthy couple by normal vaginal delivery. Birth weight was 3.85 kg. He was first referred with respiratory distress and poor feeding. During the workup of the infant in the ward, his respiratory tract showed colonization of micro-organisms including *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. His condition deteriorated and he was transferred to intensive care unit for assisted respiration for five days. Abdominal X-rays showed wide spread calcifications suggestive of meconium peritonitis. The patient was administered intravenous antibiotic therapy and his condition gradually improved. Sweat chloride concentration was 100mmol/L. He was also found to be pancreatic insufficient based on the presence of steatorrhea and measurement of stool chymotrypsin activity which was done as described previously.[7] Presence of *Pseudomonas aeruginosa* in the respiratory tract, meconium peritonitis, high sweat chloride values and pancreatic insufficiency, all point towards cystic fibrosis and thus a genetic confirmation was done by *CFTR* gene analysis.

CFTR gene analysis

The protocol for *CFTR* gene screening was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, UAE University, Al Ain, UAE. A blood sample was collected and DNA was extracted from leukocytes using a reference phenol-chloroform protocol. The two most common mutations (p.S549R(T>G) and p.F508del) were initially screened as described previously,[5] but were not found. Thirty-one most frequent mutations were further screened using the CF assay (Abbot, Rungis,

France): the p.N1303K mutation was found on one allele. The search for a second mutation was then initiated using denaturing gradient gel electrophoresis (DGGE) focused on the 27 coding regions[8-9]: no additional mutation could be identified. One of the parents forefathers being from Palestine, we further screened for a large deletion removing exons 17a to 18, 3120+1kbdel8.6kb, which has been found frequent in Palestinian Arab CF patients and proposed as a founder mutation amongst Palestinian Arabs.[10-11] The boy was heterozygous for this deletion, thus carrying the [3120+1kbdel8.6kb]+[p.N1303K] genotype.

DISCUSSION

So far, it has been observed that mutations p.F508del and p.S549R(T>G) account for 88% of chromosomes in UAE and explain 95% of CF in Emirati families, almost all the reported CF patients being homozygous for either of the two mutations.[5] Moreover, the clinical phenotypes associated with both mutations were homogeneous and extremely severe, including dramatic losses of pulmonary function.

The patient described harboring the large 3120+1kbdel8.6kb deletion in the *CFTR* gene is unique and further documents the hypothesis of a founding effect of this mutation in Palestinian Arabs. 3120+1kbdel8.6kb was first identified by Lerer *et al*.[10] in four Palestinian patients. The mutation causes a deletion of exons 17a, 17b and 18. This is one of the few large deletions that have been described in the *CFTR* gene.[3] This mutation causes an in-frame deletion of 160 amino acids that are part of transmembrane domains 10-12 of the CFTR protein.[10] This mutation was later found to have a 13% prevalence in Palestinian Arabs.[11] Patients with both a homozygous state and a compound heterozygous state for this mutation have been reported with a severe phenotype.[10-11] The intragenic haplotype and the flanking markers were identical in all the chromosomes bearing the deletion in the four Arabs reported, indicating that this mutation is an ancient founder mutation.[10] The linked haplotype could not be determined in our case, as the parents were not available.

The other mutation found in this patient, p.N1303K, was first described by Osborne *et al*. in 1991.[12] Genotype-phenotype correlations clearly indicate that this mutation is severe with respect to pancreas status but conclusions on its effect on lung disease vary among studies.[13-14] The frequency of this mutation is variable among populations. It was indeed identified in homozygosity in eight Palestinian Arab CF patients, and accounted for 21% CF alleles in this population.[10]

The fact that the compound *CFTR* genotype [3120+1kbdel8.6kb]+[p.N1303K] is observed in this patient of Palestinian ancestry, together with the consideration that the deletion has only been described in Palestinian Arabs so far, further documents the hypothesis that 3120+1kbdel8.6kb is a founder mutation in Palestinian Arabs. This case report also emphasizes the importance of retrieving ancestral histories of patients with monogenic disorders, and especially in the case of CF, a disease in which patterns of *CFTR* mutations vary greatly among populations.

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