Cystic fibrosis in a boy with meconium ileus and mild clinical phenotype associated with 2183AA-G/D1152H genotype

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We report a 16-year-old boy with cystic fibrosis presenting with meconium ileus in the neonatal period who showed mild clinical phenotype later. He had sufficient pancreatic function, mild lung involvement and borderline sweat chloride levels. Analysis of the cystic fibrosis transmembrane regulator protein gene revealed the rare mutation: 2183AA-G/D1152H. To our knowledge, this is the first report concerning such a mutation combination in cystic fibrosis.

Key words: cystic fibrosis, mutation, phenotype, 2183AA-G/D1152H.

Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population. The clinical course of the disease varies widely, with some patients dying very young because of meconium ileus (MI) or respiratory complications, while others have a mild form of the disease and have better overall survival with few symptoms[1]. Some CF transmembrane regulator (CFTR) protein mutations lead to mild, atypical (nonclassic) CF phenotype with normal or borderline sweat test results, pancreatic sufficiency (PS), and usually late-onset or more slowly progressive lung disease[2]. These patients have at least one copy of a mutant gene that confers partial function of the CFTR protein, and usually do not have overt signs of maldigestion and MI history[2].

We report a 16-year-old boy with CF presenting with MI in the neonatal period, but who then showed nonclassic CF phenotype with PS, mild lung involvement and borderline sweat chloride levels. Analysis of the CFTR gene revealed the rare mutation 2183AA-G/D1152H. In this report, we present his genotypic and clinical features. To our knowledge, this is the first report concerning such a mutation combination in CF.

Case Report

A Caucasian, Turkish boy, born as the first child of unrelated parents, was operated for MI at 3 days of age and was admitted to our hospital on the 21st day. He had no known family history for CF. In the neonatal period, his sweat chloride was 80 and 150 mEq/L and CF was diagnosed. Ventricular septal defect was detected in that period. On repeated occasions, his sweat test was measured as 44 and 50 mEq/L. He had no respiratory symptoms (no lung infections or colonization with CF pathogens in various cultures) or pancreatic or hepatic involvement in the close follow-up until 16 years of age. To date, he has not received any treatment.

Analysis of the CFTR gene revealed 2183AA-G/D1152H mutations in our patient. The patient is under regular follow-up and is now 16 years old. On his last visit, thorax computerized tomography (CT) revealed subsegmental atelectasis in medial segment of right middle and anterobasal segment of left lower lobe; bronchiectasis was not detected. His forced expiratory volume in 1 sec (FEV1) was 67% and his body mass index was 30 kg/m^2. His fecal fat loss was below 7% upon 72 h fecal fat analysis, so he was determined as having adequate pancreatic exocrine function and to date has not needed pancreatic enzyme replacement therapy.

Discussion

Our hospital is the largest referral center in Turkey and our data on CF may represent the situation for the Turkish population. In Turkish

CF patients, the most common mutation is delta F508 (28.4%), while the other mutations account for a further 6.7% of the alleles[3].

In our patient, analysis of the CFTR gene revealed 2183AA-G/D1152H mutations; this mutation combination was found for the first time.

D1152H mutation is an exon 18 mutation that causes nonclassic CF phenotype even if severe mutation (e.g. delF508) is on the other allele[4,5]. The 2183AA-G mutation in exon 13 was first described in three Canadian CF patients[6] and later was shown to have a significant frequency in patients from mid- and southern Europe. In 2000, Kılınç et al.[5] identified three homozygotes Turkish and nine compound heterozygous Spanish and Bulgarian patients for 2183AA-G mutation. These nine patients carried delF508, G542X, G1244E and 2789+5G-A on the other CF allele. All homozygote and heterozygote patients had pancreatic insufficiency (PI), recurrent lung problems and malnutrition[5], and two of the delF508/2183AA-G patients had MI. It is well known that mild mutations usually have a dominant effect because they are associated with residual exocrine function and with PS, even in patients bearing a severe mutation on the other allele[1,7,8]. On the other hand, the clinical presentation in 2183AA-G mutation is also severe in the compound heterozygote even with mild mutations[5,6]. To our knowledge, our patient is the first reported case concerning mild phenotype with 2183AA-G/D1152H mutations.

Currently, pancreatic status of CF patients appears to be primarily determined by genetic factors and is closely related to the CFTR genotype[1,9]. CF patients with MI commonly present with PI or they develop PI findings later in childhood[9]. The interesting feature in our patient was that he presented with MI in the neonatal period; however, to date he has no evidence of PI. Lands et al.[10] reported two infants with CF presenting with MI, who had no clinical or biochemical evidence of PI. They documented reduced enzyme secretions and severely limited fluid secretory capacity of the pancreas in both patients, even when clinical PI was absent. They speculated that impaired fluid secretion (dehydration of the fetal intestine) may be a more significant factor than pancreatic proteolytic deficiency in the pathogenesis of MI in some cases. Since MI has been described in infants with little or no pancreatic involvement and MI in CF does not necessarily imply PI, enzyme therapy is not recommended routinely in these patients[11]. Although pancreatic status is closely related to the CFTR genotype, MI can be influenced by factors other than the CFTR genotype, which might explain why these two clinical features are separate in some cases[1].

Evans et al.[12] and Lai et al.[13] investigated the impact of MI on the clinical course of children with CF, and they suggested that MI is an indicator of a more severe phenotype of CF. In this regard, our case is quite exceptional with his phenotypic features.

In conclusion, we present our CF patient having 2183AA-G/D1152H mutations with a history of MI and nonclassic CF phenotype. To our knowledge, this is the first reported case showing a mild phenotype with such a combination of mutations. Such distinctive cases and their genotypic and phenotypic features could also be explained by the presence or absence of modifier genes.

REFERENCES

1. Salvatore F, Scudiero O, Castaldo G. Genotype-phenotype correlation in cystic fibrosis: the role of modifier genes. Am J Med Genet 2002; 111: 88-95.
2. Knowles MR, Durie PR. What is cystic fibrosis? N Engl J Med 2002; 347: 439-442.
3. Yilmaz E, Erdem H, Ozguc M, et al. Study of 12 mutations in Turkish cystic fibrosis patients. Hum Hered 1995; 45: 175-177.
4. Lebecque P, Leal T, Godding V. Cystic fibrosis and normal sweat chloride values: a case-report. Rev Mal Respir 2001; 18: 443-445.
5. Kılınç MO, Ninis VN, Tolun A, et al. Genotype-phenotype correlation in three homozygotes and nine compound heterozygotes for the cystic fibrosis mutation 2183AA->G shows a severe phenotype. J Med Genet 2000; 37: 307-309.
6. Bozon D, Zielenski Z, Rininsland F, Tsui LC. Identification of four new mutations in the cystic fibrosis transmembrane conductance regulator gene: I148T, L1077P, Y1092X, 2183AA->G. Hum Mutat 1994; 3: 330-332.
7. Kerem E, Corey M, Kerem B, Durie P, Tsui LC, Levison H. Clinical and genetic comparison of patients with cystic fibrosis, with or without meconium ileus. J Pediatr 1989; 114: 767-773.
8. Walkowiak J, Herzig KH, Witt M, et al. Analysis of exocrine pancreatic function in cystic fibrosis: one mild CFTR mutation does not exclude pancreatic insufficiency. Eur J Clin Invest 2001; 31: 796-801.
9. Campbell PW, Phillips JA. The cystic fibrosis gene and relationships to clinical status. Semin Respir Infect 1992; 7: 150-157.

10. Lands L, Zinman R, Wise M, Kopelman H. Pancreatic function testing in meconium disease in cystic fibrosis: two case reports. J Pediatr Gastroenterol Nutr 1998; 7: 276-279.

11. MacLusky I, Levison H. Cystic fibrosis. In: Chernick V, Boat TF, Kendig EL (eds). Kendig's Disorders of the Respiratory Tract in Children (6th ed). Philadelphia: WB Saunders; 1998: 838-883.

12. Evans AK, Fitzgerald DA, McKay KO. The impact of meconium ileus on the clinical course of children with cystic fibrosis. Eur Respir J 2001; 18: 784-789.

13. Lai HJ, Cheng Y, Cho H, Kosorok MR, Farrell PM. Association between initial disease presentation, lung disease outcomes, and survival in patients with cystic fibrosis. Am J Epidemiol 2004; 159: 537-546.