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Case Studies

Clinical presentation of mild cystic fibrosis in a Serbian patient homozygous for the CFTR mutation c.1393-1G>A

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Abstract

We present a case of a 19-year old male with uncommon initial clinical cystic fibrosis (CF) presentation and a rare CFTR genotype, homozygote for c.1393-1G>A mutation (legacy name 1525-1G>A).

1. Case report

The boy of Caucasian origin (Serbian) was born to healthy non-consanguineous parents at term following a healthy pregnancy with neonatal jaundice and no perinatal complications. Birth weight was 3.1 kg and length 51 cm. The child was exclusively breastfed for 4 months, after which he received complementary foods and continued breastfeeding until he was 2 years old. He did well in the neonatal period and did not manifest any respiratory or other problems, except for the excessive fat in stool after 2 years of age. Two older children of the same parents (both male) died at breastfeeding age, one due to pneumonia (8 months old) and the other of sudden infant death syndrome (9 months old). It is probable that they suffered from CF, but no molecular diagnostics was performed in these cases. The boy's parents and grandparents are of Serbian origin.

The patient was hospitalized for the first time due to liver steatosis confirmed by ultrasonography at the age of 7. On admission a height of 115.5 cm and a body weight of 20.5 kg were reported. Physical examination findings were normal. Laboratory analyses revealed low cholesterol (2.97 mmol/L) and triglyceride (0.41 mmol/L) serum levels. Values for liver function tests, blood gas analyses and standard blood test were within the normal range, as well as levels of total protein, albumins, alkaline phosphatase, urea, glycemia, sodium, potassium, chloride, iron, calcium and phosphorus. Chest X-ray showed expanded interstitium, with no signs of hyperinflation. Findings on otorhinolaryngological examination were normal, as well as on echocardiogram and electrocardiogram. Pathohistological examination showed no abnormalities in the duodenal epithelium. Ultrasonographical examination indicated liver steatosis, but no evidence of hepatomegaly. The CF was suspected due to the liver steatosis, which represents a rather uncommon way to diagnose CF. Elevated sweat test of 110 mmol/L was diagnostic of CF (normal values <40 mmol/L, borderline values 40–60 mmol/L). Routine genetic analysis did not detect presence of any of the most common CFTR mutations. In order to screen the CFTR gene for other mutations, all 27 exons (along with their flanking regions) were analyzed by PCR and direct DNA sequencing. Splicing mutation c.1393-1G>A on a haplotype background TG10-T9 was detected in the homozygous state, and both parents were confirmed to be mutation carriers. Upon diagnosis, adequate diet and therapeutic measures were introduced: pancreatic enzyme

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replacement therapy (Creon) with every meal and restriction of long-chain triglycerides and supplementation of essential fatty acids, medium-chain triglycerides, liposoluble vitamins (A, D, E) and sodium chloride. The patient was apparently healthy until the age of 12.

At the age of 12 mild chronic bronchitis (without pneumonia or sinusitis) and cholestasis manifested. Ultrasonographical examination of the abdomen indicated persistent liver steatosis without hepatomegaly. Except for lower concentration of serum triglycerides (0.7 mmol/L), other laboratory analyses, including cholesterol levels, were within the reference range. The patient has also developed signs of mild cholestasis, with elevated levels of gamma glutamyl transpeptidase (GGT 83 U/L; normal value <50 U/L) and alkaline phosphatase (ALP 1402 U/L; normal value <1200 U/L). Laboratory findings were also indicative of hepatocyte lysis, with elevated alanine aminotransferase (ALT 107 U/L; normal value <50 U/L) and aspartate aminotransferase (AST 72 U/L, normal value <46 U/L). Other laboratory findings (including bilirubin, PT, PTT and creatine phosphokinase) were within reference range.

At the age of 17 the patient had no subjective health problems, but on physical examination signs of mild obstructive bronchitis and emphysema were found and clubbing fingers were observed. Chest X-ray showed expanded interstitium with signs of mild emphysema, as well as signs of hyperinflation and fibrosis (Fig. 1). Chest CT scan showed apical and posterior condensation of the right upper lobe. Tubular and cystic bronchiectases with obliteration and inflammation of bronchioles were observed, as well as dorsal bilateral pleural adhesions of upper lobes. Spirometry showed significant decrease of airflow (FVC 35% and FEV1 40%). The number of leukocytes in induced sputum showed 5% of eosinophils, 48% of neutrophils, 12% of lymphocytes, 10% of monocytes and 25% of macrophages. Laboratory findings were within normal values, except for mild cholestasis with non-progressive course.

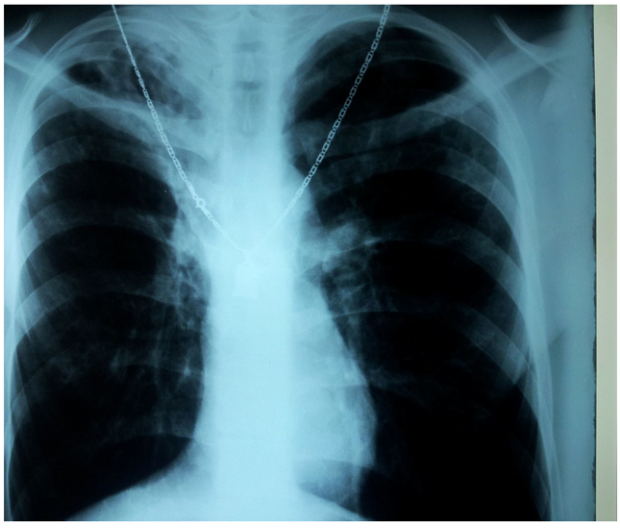

Fig. 1. Chest X-ray showing expanded interstitium with signs of mild emphysema, hyperinflation and fibrosis.

At the age of 19 the patient was referred to the pulmonary department due to repeated respiratory exacerbations and frequent obstructions with cough and morning sputum production. After pulmonary reevaluation the following therapy was administered: inhaled gentamicin, ibuprofen, pulmosine and postural drainage, with antibiotic therapy for *Haemophilus* (15 days, IV) and switch antibiotic therapy (15 days, per os). After exacerbation was treated pulmonary findings returned to normal (FEV1 55% and FVC 53%), the bronchodilator test was positive and the patient remains on a fixed combination of inhaled corticosteroids and beta 2 agonists with aminoglycoside inhalations.

2. Discussion

With the exception of the most common mutation c.1521_1523delCTT (legacy name F508del), the vast majority of CFTR mutations are rare or restricted to certain populations and their influence on clinical phenotype is understudied [1]. Splicing mutation c.1393-1G>A was first described in 1993 in a CF patient of Indo-Iranian origin with severe gastrointestinal and pulmonary disease [2]. To date, this mutation has been found almost exclusively in patients of Asian origin in compound heterozygotes with a severe form of CF [3–5].

Molecular characterization has shown that the transcript product of c.1393-1A allele results from splicing between the intron 9 donor and the intron 10 acceptor [5]. Since exon 10 codes for a large proportion of the first nucleotide binding domain (NBD1) of the CFTR protein, essential for the function of the protein, its absence can cause substantial changes in protein structure and such mutants show major defects in channel opening. Therefore, the consequences of the c.1393-1G>A mutation resemble those of the c.1521_1523delCTT mutation, also located in NBD1.

The influence of the mutation c.1393-1G>A on CF clinical phenotype was studied only in compound heterozygotes with the mutation c.1521_1523delCTT [5]. In such cases, functional analysis showed that CFTR function is defective in native tissues from c.1393-1G>A/c.1521_1523delCTT patients. In compound heterozygotes described so far in the literature the CF clinical presentation was typical, with respiratory problems and pancreatic insufficiency, and they were diagnosed until the age of 5 [1,3]. The homozygous patient described here differs in most aspects of clinical presentation from the compound heterozygotes: the main symptom at diagnosis was liver disease, pancreatic insufficiency was mild and well controlled, and respiratory problems were occasional during the first 18 years of life. Exocrine pancreatic insufficiency was compensated by breastfeeding for two years after birth and consistent treatment, which explain the patient's satisfactory growth and development until initial admission. Prior to puberty, which was not delayed, he has gradually developed respiratory problems and cholestasis. The patient was not on preventive pulmonary therapy until 19 years of age due to the fact that respiratory problems were occasional and spirometry results were within normal range.

An uncommon initial clinical presentation and disease course in this rare CFTR genotype may contribute to the understanding of the influence the mutation c.1393-1G>A has

on CF clinical phenotype. No homozygotes for this mutation have been reported so far and functional analyses performed on c.1393-1G>A mutation did not include this mutation in a homozygous state. This report indicates that there may be a phenotype difference between homozygotes and compound heterozygotes for this mutation. Further clinical and functional studies are needed to resolve this question.

Acknowledgments

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